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(13) New substituted azetidinones as anti-inflammatory and antidegenerative agents.

(14) New substituted azetidinones are found to be potent elastase inhibitors and thereby useful anti-inflammatory/antidegenerative agents.

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NEW SUBSTITUTED AZETIDINONES AS ANTI-INFLAMMATORY AND ANTIDEGENERATIVE AGENTS

BACKGROUND OF THE INVENTION

We have found that a group of new substituted azetidinones are potent elastase inhibitors and therefore are useful anti-inflammatory/antidegenerative agents.

5 Proteases from granulocytes and macrophages have been reported to be responsible for the chronic tissue destruction mechanisms associated with inflammation, including rheumatoid arthritis and emphysema. Accordingly, specific and selective inhibitors of these proteases are candidates for potent anti-inflammatoty agents useful in the treatment of inflammatory conditions resulting in connective tissue destruction, e.g. rheumatoid arthritis, emphysema, bronchial inflammation, osteoarthritis, spondylitis, lupus, 10 psoriasis, atherosclerosis, sepsis, septicemia, shock, periodontitis, cystic fibrosis and acute respiratory distress syndrome.

The role of proteases from granulocytes, leukocytes or macrophages are related to a rapid series of events which occurs during the progression of an inflammatory condition:

15 (1) There is a rapid production of prostaglandins (PG) and related compounds synthesized from arachidonic acid. This PG synthesis has been shown to be inhibited by aspirin-related nonsteroidal anti-inflammatory agents including indomethacin and phenylbutazone. There is some evidence that protease inhibitors prevent PG production;

20 (2) There is also a change in vascular permeability which causes a leakage of fluid into the inflamed site and the resulting edema is generally used as a marker for measuring the degree of inflammation. This process has been found to be induced by the proteolytic or peptide cleaving activity of proteases, especially those contained in the granulocyte, and thereby can be inhibited by various synthetic protease inhibitors, for example, N-acyl benzisothiazolones and the respective 1,1-dioxides. Morris Zimmerman et al., J. Biol. Chem., 255, 9848 (1980); and

25 (3) There is an appearance and/or presence of lymphoid cells, especially macrophages and polymorphonuclear leukocytes (PMN). It has been known that a variety of proteases are released from the macrophages and PMN, further indicating that the proteases do play an important role in inflammation.

In general, proteases are an important family of enzymes within the peptide bond cleaving enzymes whose members are essential to a variety of normal biological activities, such as digestion, formation and 30 dissolution of blood clots, the formation of active forms of hormones, the immune reaction to foreign cells and organisms, etc., and in pathological conditions such as the degradation of structural proteins at the articular cartilage-pannus junction in rheumatoid arthritis etc.

Elastase is one of the proteases. It is an enzyme capable of hydrolyzing the connective tissue component elastin, a property not contained by the bulk of the proteases present in mammals. It acts on a 35 protein's nonterminal bonds which are adjacent to an aliphatic amino acid. Neutrophil elastase is of particular interest because it has the broadest spectrum of activity against natural connective tissue substrates. In particular, the elastase of the granulocyte is important because, as described above, granulocytes participate in acute inflammation and in acute exacerbation of chronic forms of inflammation which characterize many clinically important inflammatory diseases.

40 Proteases may be inactivated by inhibitors which block the active site of the enzyme by binding tightly thereto. Naturally occurring protease inhibitors form part of the control or defense mechanisms that are crucial to the well-being of an organism. Without these control mechanisms, the proteases would destroy any protein within reach. The naturally occurring enzyme inhibitors have been shown to have appropriate configurations which allow them to bind tightly to the enzyme. This configuration is part of the reason that 45 inhibitors bind to the enzyme so tightly (see Stroud, "A Family of Protein-Cutting Proteins" Sci. Am. July 1974, pp. 74-88). For example, one of the natural inhibitors, α_1 -Antitrypsin, is a glycoprotein contained in human serum that has a wide inhibitory spectrum covering, among other enzymes, elastase both from the pancreas and the PMN. This inhibitor is hydrolyzed by the proteases to form a stable acyl enzyme in which the active site is no longer available. Marked reduction in serum α_1 -antitrypsin, either genetic or due to 50 oxidants, has been associated with pulmonary emphysema which is a disease characterized by a progressive loss of lung elasticity and resulting respiratory difficulty. It has been reported that this loss of lung elasticity is caused by the progressive, uncontrolled proteolysis or destruction of the structure of lung tissue by proteases such as elastase released from leukocytes. J. C. Powers, TIBS, 211 (1976).

Rheumatoid arthritis is characterized by a progressive destruction of articular cartilage both on the free

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surface bordering the joint space and at the erosion front built up by synovial tissue toward the cartilage. This destruction process, in turn, is attributed to the protein-cutting enzyme elastase which is a neutral protease present in human granulocytes. This conclusion has been supported by the following observations:

(1) Recent histochemical investigations showed the accumulation of granulocytes at the 5 cartilage/pannus junction in rheumatoid arthritis; and

(2) a recent investigation of mechanical behavior of cartilage in response to attack by purified elastase demonstrated the direct participation of granulocyte enzymes, especially elastase, in rheumatoid 10 cartilage destruction. H. Menninger et al., in Biological Functions of Proteinases, H. Holzer and H. Tschesche, eds. Springer-Verlag, Berlin, Heidelberg, New York, pp. 196-206, 1979.

Accordingly, an object of this invention is to discover new protease inhibitors, especially elastase 15 inhibitors, useful for controlling tissue damage and various inflammatory or degenerative conditions mediated by proteases particularly elastase.

Another object of the present invention is to provide pharmaceutical compositions for administering the 20 active substituted azetidinones as protease inhibitors especially human leukocyte elastase.

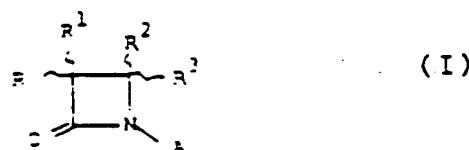
Still a further object of this invention is to provide a method of controlling inflammatory conditions by administering a sufficient amount of one or more of the active, substituted azetidinones in a mammalian species in need of such treatment.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to potent elastase inhibitors of formula (I) which are useful in the prevention, control and treatment of inflammatory/degenerative conditions especially arthritis and emphysema.

A large number of the azetidinone derivatives of formula (I) are known antibiotics which have been described in patents and various publications.

The formula of the substituted azetidinones which are found to exhibit anti-inflammatory and anti-degenerative activities by the present invention are represented as follows:



35 wherein

R can be at the α or the β -position and is hydrogen, straight or branched loweralkyl especially C₁-₆alkyl, such as methyl, ethyl, n- or i-propyl, butyl, pentyl or hexyl; or loweralkyl substituted with a radical

40 R' as defined below; or halo such as fluoro, chloro or bromo;

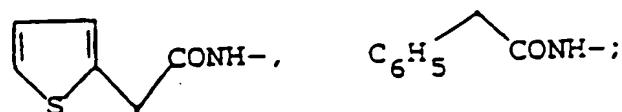
R' can be at the α - or the β -position and is

(1) OB or -S(O)_nB wherein B is as defined below and n is 0, 1 or 2;

(2) Straight or branched loweralkenyl especially C₂-₆alkenyl such as vinyl, allyl, -CH₂CH=CH(CH₃)₂, and -CH₂CH₂CH=CH₂;

(3) loweralkyl as defined above;

(4) acylamino e.g.

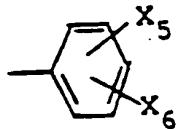


55 or

(5) amino:

(6) Straight or branched loweralkynyl group especially C₃-5 alkynyl such as -C≡CH, -CH₂-C≡CH and -CH₂CH₂-C≡CCH₃;
 (7) An aryl group having 6-14 carbon atoms as described below such as phenyl of formula

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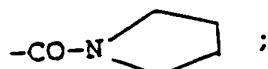
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wherein X₅ and X₆ independently are:

- 1) Q, where Q is H, loweralkyl, haloloweralkyl, phenyl or substituted phenyl as previously defined, or naphthyl;
- 2) halo.
- 3) loweralkenyl;
- 4) loweralkynyl;
- 5) -SQ;
- 6) -OO:
- 7) -CHQCOO¹, where Q¹ is defined as Q and Q¹ can be the same as or different from Q;
- 8) -CHQCOOQ¹ such as CH₂COOH;
- 9) -CH₂SQ;
- 10) -CHQSQ¹:
- 11) -CH₂OQ or -CHQOQ¹ especially -CH₂OH and -CH₂OCH₃;
- 12) -COQ for example, -COCH₃ and -(CO)H;
- 13) -COOQ especially -COOH and COOt-Bu;
- 14) -OCOQ such as -OCOCH₃;
- 15) -NQQ¹;
- 16) -NQCOQ¹ especially -NHCOCH₃;
- 17) -CH₂NH₂ or -CH₂N(CH₃)₃I⁻;
- 18) -CH₂OCOCH₃;
- 19) -NQSO₂Q¹;
- 20) -SO₂NQQ¹;
- 21) -SOQ:
- 22) -SO₂Q:
- 23) -SO₃Q:
- 24) -CN:
- 25) -NO₂:
- 26) -CONQQ¹:
- 27) -NO:
- 28) -CSQ:
- 29) -CSNQQ¹:
- 30) -CF₂SQ:
- 31) -CF₂OQ:

40 32) -NQCONHQ¹ or NQCONQ¹Q² where Q² is defined as Q¹ and Q² can be the same as or different from Q¹;

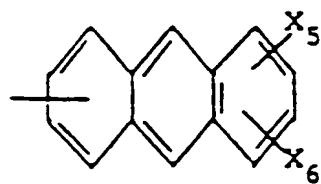
- 33) -CH₂Y wherein Y represents -CH(NHAC)COO⁻, CH(NH₂)COO⁻, CH₂COOH, COOH, -N(CH₃)₂, OH, CH₂N(CH₃)₂, or CH₂OH;
- 34) -CH(C₁-C₅ alkyl);
- 35) -NH(CO)CH₂CH₂COOH;
- 36)



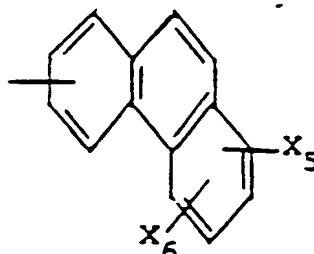
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or

37) -CO-NH-SO₂phenyl or substituted phenyl such as p-chlorophenyl;



or

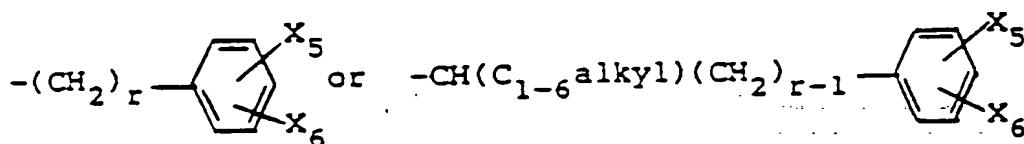


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- (d) cycloalkyl having from 3 to 8 carbon atoms especially cyclopropyl, cyclopentyl or cyclohexyl;
- (e) straight or branched alkenyl having from 2 to 20 carbon atoms, for example, allyl;
- (f) straight or branched alkynyl having from 2 to 20 carbon atoms, for example, $\text{-C}\equiv\text{CH}$;
- (g) aralkyl, alkaryl, aralkenyl, aralkynyl, alkenylaryl or
25 alkynylaryl wherein alkyl, aryl, alkenyl and alkynyl are as previously defined for example, $\text{C}_1\text{-alkylphenyl}$ of formula

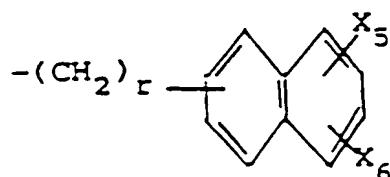
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wherein r is 1 to 6. $\text{C}_1\text{-alkyl naphthyl}$ of formula

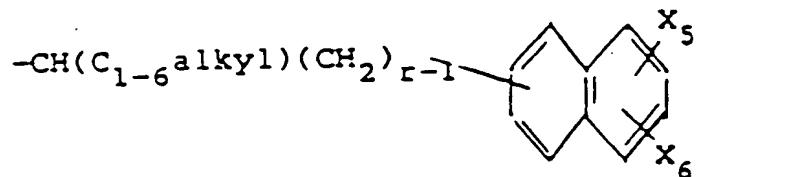
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or

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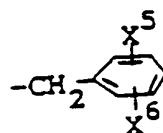


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- (h) heteroaryl comprising monoheteroaryl, di- or polyheteroaryl, or fused heteroaryl containing from 1 to 3 of any one or more of the heteroatoms N, S or O in each heteroaryl ring thereof, for example, pyridyl, pyrrolyl, such as

8) heteroaryl such as unsubstituted or substituted furyl, thienyl, thiazolyl, pyrrolyl, pyrimidinyl, pyridyl, oxazolyl, tetrazolyl or imidazolyl wherein the substituents are as those described for substituted phenyls;
 9) aralkyl especially phenyl C₁₋₆alkyl such as benzyl of formula

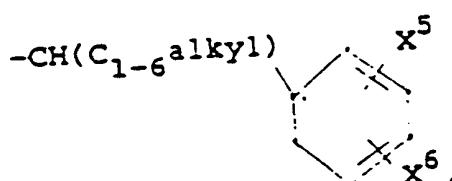
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or

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or phenethyl:

(10) halo such as F, Cl, Br or I;

(11) N₃;

(12) hydrogen;

25 (13) R and R' may join together and form a cycloalkyl such as a C₃₋₅cycloalkyl, e.g., cyclopentane.
 =C(B)(B₁) or =O (oxo) wherein B and B₁ independently are as defined below:(14) -CH₂OC-alkyl especially -CH₂OCH₃ and -CH₂OC₂H₅;(15) -CH₂CH₂OC-alkyl especially -CH₂CH₂OCH₂H₅;30 R² and R³ can be at the α or the β-position and independently are

(1) B as defined below;

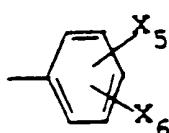
(2) -CONBB- wherein B and B₁ independently represent

(a) H;

(b) straight or branched alkyl having from 1 to 20 carbon atoms, preferably C₁₋₅alkyl such as methyl, ethyl, isopropyl, t-butyl, pentyl or hexyl;

35 (c) aryl having from 6 to 14 carbon atoms such as phenyl or substituted phenyl of formula

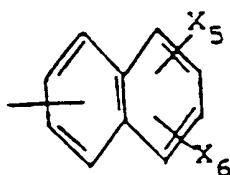
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naphthyl or substituted naphthyl of formula

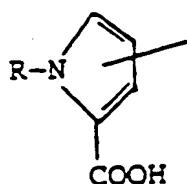
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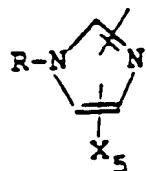
or anthracyl or substituted anthracyl of formula

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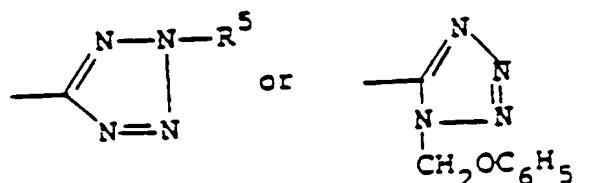


thienyl, isothiazolyl, imidazolyl such as
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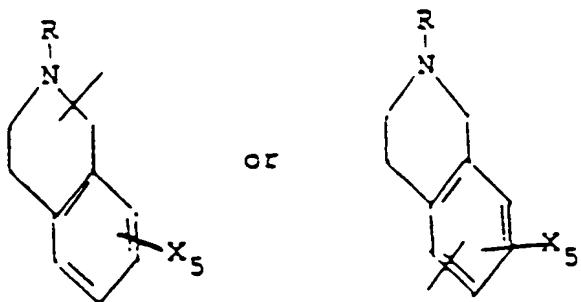


20 tetrazolyl such as
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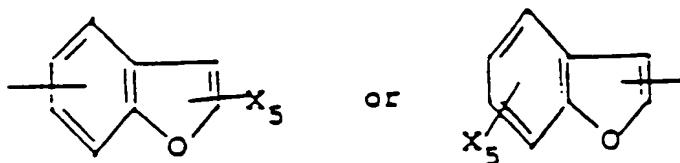
30 pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, tetrahydroisoquinolyl such as
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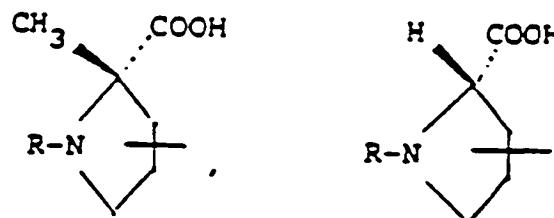
benzothienyl, benzofuryl such as

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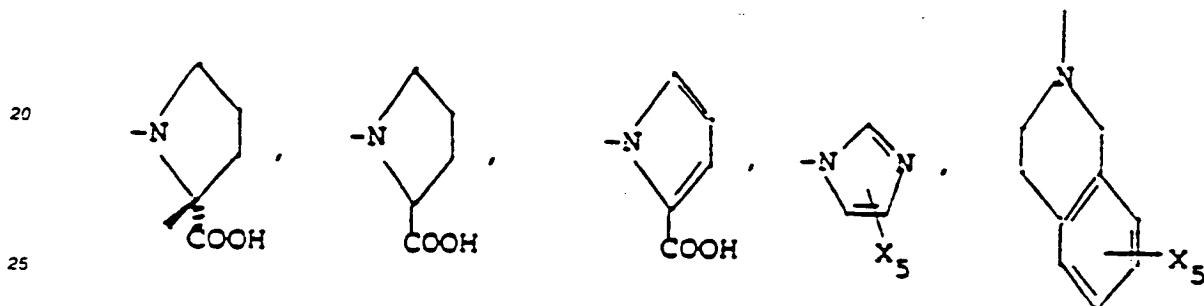
pyrazolyl, indolyl, purinyl, carbazolyl, isoxazolyl and the like:
(i) heteroarylalkyl such as 2-pyridylmethyl, 2-thienylmethyl and 3-isothiazolylethyl; or
(j) heterocycloalkyl e.g., 1,3-dioxacyclohex-4-yl, piperidino.

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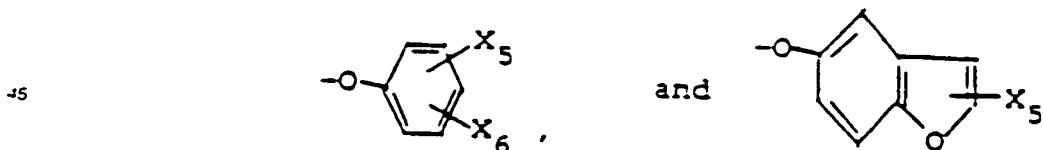
10 morpholino, oxacyclopropyl, pyrrolidino, benzothiazolino, imidazolidino, pyrazolidino, and piperazino;
 (k) heterocycloalkenyl such as pyrrolino, 2-imidazolino, 3-pyrazolino or isoindolino;
 (l) B and B₁ joined together and form a heterocyclic ring containing at least one N-atom and optionally 1 to
 3 of the heteroatoms, N, S, or O, e.g.,

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the above groups (a)-(l) can be unsubstituted or can be substituted by one or more radical R⁴ selected from
 30 the group consisting of loweralkyl, hydroxy, aryloxy, alkoxy, halo, nitro, loweralkylthio, arylthio, mercapto, amino, monoalkyl or dialkyl substituted amino, cyano, carboxy, loweralkanoyl, Ar(C=O), aminosulfonyl, aminosulphenyl, aminosulfinyl, carbamoyl, carbamoyloxy, -S(O)_qR⁵, SO₃R⁵, -P(O)_qR⁵ (where q is 1 or 2 and R⁵ is H, C₁-₆ alkyl, aralkyl or aryl as previously defined), azido, carboxamido or N-substituted carboxamido;

35 (3) -S(O)_nB;
 (4) -S(O)_nNBB₁;
 (5) -N(B)S(O)_nB₁;
 (6) -P(O)_qBB₁;
 (7) -C(O)B especially acetyl, benzoyl, e.g., p-chlorobenzoyl, p-methylbenzoyl and p-aminosulfonylbenzoyl;
 40 (8) -OB especially -OC₁-₆alkyl, phenoxy or substituted phenoxy of formula

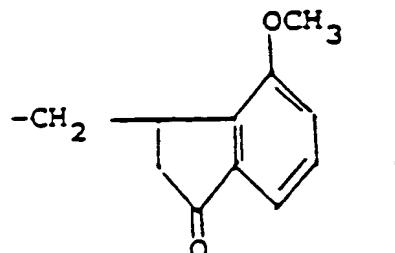


50 (9) -COOB, -OC(O)OB or OC(O)NBB₁;
 (10) -O-C(O)-B especially C₁-₆ alkanoyloxy such as acetoxy;
 (11) cyano;
 (12) -S-C(O)-B especially C₁-₆ alkanoylthio such as acetylthio; or
 (13) R² and R³ may join and form =C(B₁)(B), a C₁-₆cycloalkyl for example, cyclopentyl, and =O-(OXO);

55 A is
 (1) -O-C(O)-B;
 (2) -S(O)_nB;
 (3) -S(O)_nNBB₁;

(4) -C(O)B;
 (5) SO₃-M wherein M represents
 (a) an alkali anion such as Na⁻, K⁻; or
 (b) a quaternary ammonium group of formula N⁺(R⁵)₄, for example, (n-Bu)₄N⁺
 5 (6) substituted or unsubstituted phosphoryl or phosphonyl such as -P(O)₃(R⁵)₂ or -P(O)₄R⁵;
 (7) -C(O)NBB₁ especially -CON(C₂H₅)Phenyl and -CONHB₁, wherein B₁ is
 (a) -(CH₂)_rPh, or CH(C₁-alkyl)(CH₂)_{r-1}Ph, e.g., -CH(C₂H₅)-Ph, -CH(C₃H₇)-Ph, -CH-(allyl)-Ph, -CH(C₂H₅)-CH₂Ph, or -CH(CH₃)-Ph wherein Ph represents phenyl or substituted phenyl as previously defined, for examples, 4-methyl-phenyl, 4-methoxyphenyl, 4-N,N-dimethyl-amino-phenyl, 4-benzoyloxy-phenyl, 4-phenyl-phenyl, 3,4-methylenedioxy-phenyl, and 3,4-dimethyl-phenyl;
 10 (b) -(CH₂)_r(Naph) especially -CH₂(Naph) or -CH(C₂H₅)(Naph) wherein (Naph) is α or β -naphthyl or substituted naphthyl as previously defined;
 (c) -(CH₂)_r(Ar) especially -CH₂CH₂Ar or -CH₂Ar wherein Ar represents heteroaryl especially 2-thienyl, 2-furyl, 3-thienyl, or benzofuryl;
 15 (d) -(CH₂)_rOPh especially -CH₂CH₂CH₂OPh;
 (e) -(CH₂)_rCH(OH)Ph;
 (f) -(CH₂)_r(CO)Ph;
 (g)

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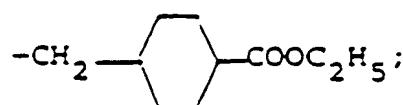
30 (h)



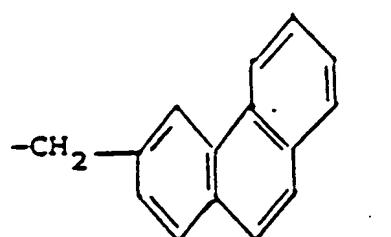
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(i) -CH₂-Ph(p-CO-NH-SO₂-Ph(p-Cl));
 (j)

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(k)

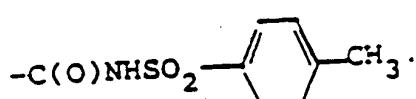
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or

(I) -CH(CH₃)-Ph(p-cyclohexyl):(8) -C(O)OB especially C₁-s alkoxycarbonyl, e.g., methoxycarbonyl, and -ethoxycarbonyl or COOCH₂-Ph(p-COOC₂H₅):(9) halo C₁-s alkyl such as trifluoromethyl;(10) -OB especially -O-CH₂-(phenyl or substituted phenyl as previously defined), for example,5 -OCH₂C₆H₅; -OCH₂C₆H₄-OCH₃; or OCH₂C₆H₄NO₂:(11) silyl such as -Si(CH₃)₂(t-Bu):(12) B especially H, C₁-s alkyl, CH₂OH, -CH₂O(CO)CH₃, phenyl or substituted phenyl, -CHR⁵L whereR⁵ is as previously defined and L is a good leaving group comprising OAc, SAC, halogen, OR⁵, SR⁵, SOR⁵,10 SO₂R⁵, OTs, OCOCF₃, and mesyl wherein Ac is acetyl; and Ts is tosyl; or

(13)



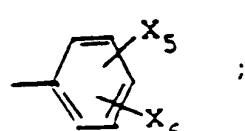
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Preferably, the compounds of the present invention are of formula (I) wherein:

20 R is hydrogen; or C₁-s alkyl:R¹ is(1) C₁-s alkyl especially methyl or ethyl(2) OR⁵:

(3) phenyl of formula

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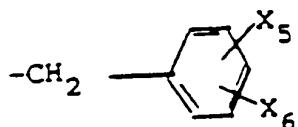


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(4) hydrogen:

(5) benzyl of formula

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(6) CH₂OC₁-s alkyl or -CH₂CH₂OC₁-s alkyl:(7) C₂-s alkenyl; or45 (8) R and R¹ may join together and form a cyclopentane:R² and R³ independently are

(1) hydrogen:

(2) S(O)_nR³:

(3) COOB:

50 (4) CONBB¹:

(5) OB:

(6) C₁-s alkyl:

(7) phenyl or substituted phenyl as previously defined:

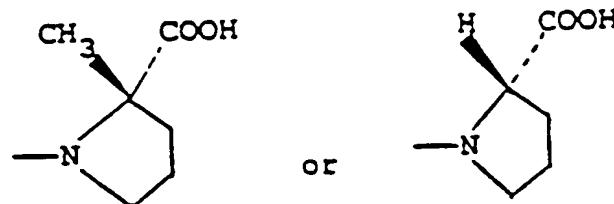
(8) naphthyl as previously defined:

55 (9) cyclohexyl:

(10) benzyl as previously defined:

(11) heteroaryl selected from a group consisting of imidazolyl, benzofuryl and tetrahydroisoquinolyl:

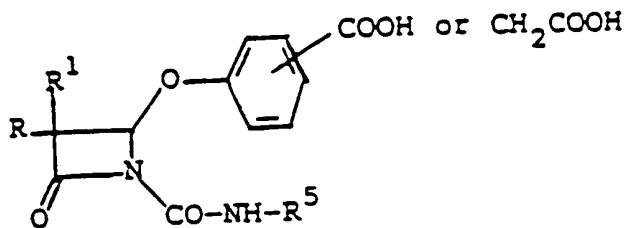
(12) heterocycloalkyl such as



10 A (13) C(O)B;
 is
 (1) SOR^s;
 (2) SO₂R^s;
 (3) COOB;
 (4) C(O)B;
 (5) CONBB₁, wherein B and B₁ independently are:
 (a) H;
 (b) C₁-_salkyl;
 (c) -(CH₂)_rPh where r represents 1 or 2 and Ph represents phenyl or substituted phenyl as previously defined;
 (d) CH(C₁-_salkyl)(CH₂)_rPh where Ph is as defined above;
 (6) phenyl or substituted phenyl as previously defined such as p-methoxyphenyl, p-nitrophenyl and p-methylphenyl;
 (7) C₁-_salkyl;
 (8) CH₂OH;
 (9) CH₂OC(O)CH₃; or
 (10) -C(O)NHSO₂-Ph(p-CH₃).

 Even more preferably, the compounds of the present invention are of formula (I) wherein
 R is hydrogen or C₁-_salkyl;
 R' is
 (1) hydrogen;
 (2) C₁-_salkyl;
 (3) C₁-_salkoxy such as methoxy;
 (4) C₂-_salkenyl;
 (5) phenyl or substituted phenyl as previously defined; or
 (6) CH₂OC₁-_salkyl;
 R² is hydrogen;
 R³ is
 (1) S(O)_nR^s;
 (2) CONBB₁;
 (3) COOB;
 (4) phenoxy or substituted phenoxy;
 (5) imidazolyl; or
 (6) substituted or unsubstituted alkoxy, for example, OCH₃ or -OCH₂CONH₂;
 A is
 (1) CO₂R^s wherein R^s is H, C₁-_salkyl, -CH₂Ph, -CH(CH₃)Ph, -CH(C₂H₅)Ph, CH(C₃H₇)Ph or CH-(C₃H₅)Ph wherein Ph represents phenyl or substituted phenyl as previously defined;
 (2) CONHR^s; or
 (3) SO₂R^s.

The most preferred compounds of the present invention are listed in the following table.



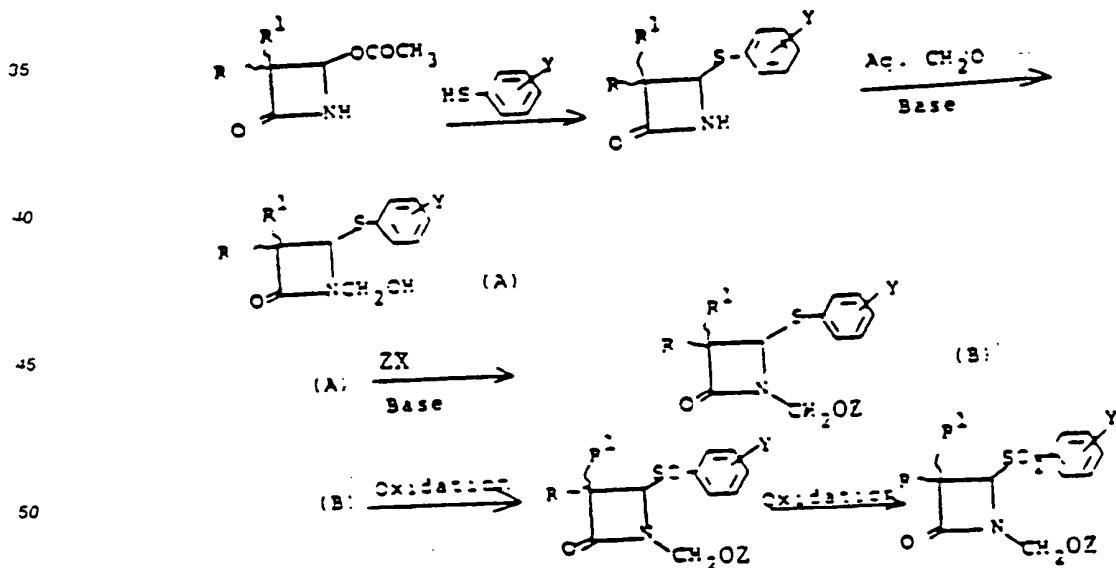
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	R	R¹	R⁵
15	C ₂ H ₅	CH ₃	CH(CH ₃)Ph
	C ₂ H ₅	C ₂ H ₅	CH ₂ -(4-Ph-Ph)
	C ₂ H ₅	CH ₃	CH(C ₂ H ₅)Ph
	C ₂ H ₅	C ₂ H ₅	CH(C ₂ H ₅)Ph
	C ₂ H ₅	CH ₂ OCH ₃	CH(C ₂ H ₅)Ph
	C ₂ H ₅	C ₂ H ₅	CH(C ₃ H ₇)-(4-CH ₃ -Ph)
	C ₂ H ₅	C ₂ H ₅	CH(C ₃ H ₅)-(4-CH ₃ -Ph)
	C ₂ H ₅	C ₂ H ₅	CH(C ₃ H ₇)Ph
	C ₂ H ₅	C ₂ H ₅	CH(C ₃ H ₇)-(3,4-methylenedioxy-Ph)
	C ₂ H ₅	C ₂ H ₅	CH(C ₃ H ₅)-(3,4-methylenedioxy-Ph)

25 In the above table, Ph represents phenyl or substituted phenyl as previously defined.
The compounds of the present invention are either known or are prepared among other methods by the following representative schemes.

30 Scheme (a)

as illustrated by Examples 16-19.



55 wherein

Y is -NO₂, -CH₃, -OCH₃, -Cl, -F, etc;

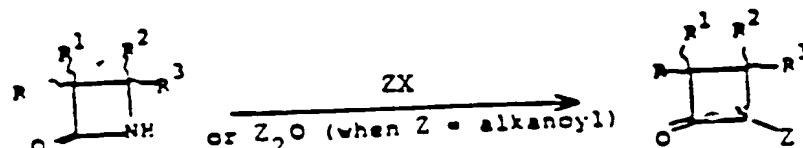
X is halo, e.g., Cl, Br or I;

Z is BCO or BSO₂.

Scheme (b)

as illustrated by Examples 1-4.

5



10

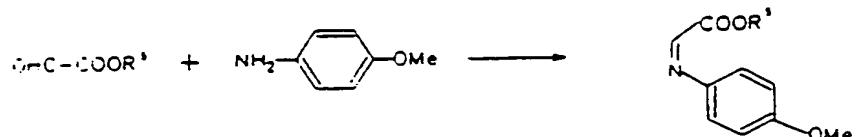
wherein

X is halo:

Z is as previously defined, e.g., $\text{-SO}_2\text{-(p-NO}_2\text{-Ph)}$, -COCH_3 , $\text{-CH}_2\text{OTs}$, etc. wherein Ph represents phenyl or
15 substituted phenyl.Scheme(c)

as illustrated by Examples 5-15

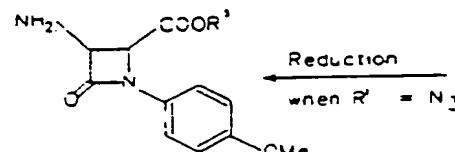
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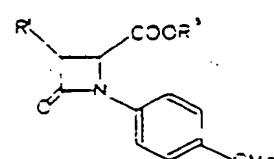
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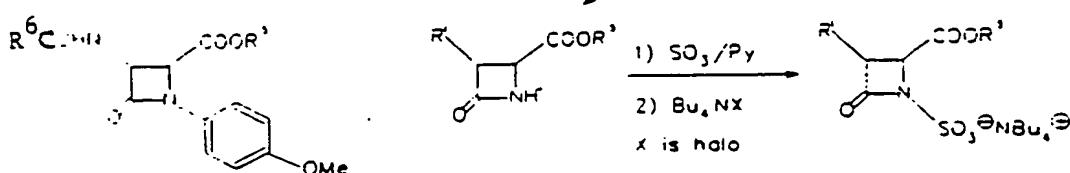
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35



40



45

wherein

R⁶ is H, CF₃, CH₃, etc.;R⁵ and R¹ are as previously defined; and

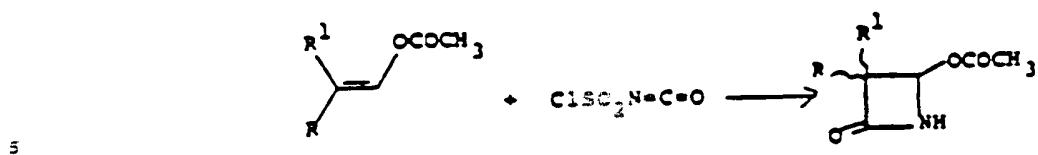
CAN is ceric ammonium nitrate.

50

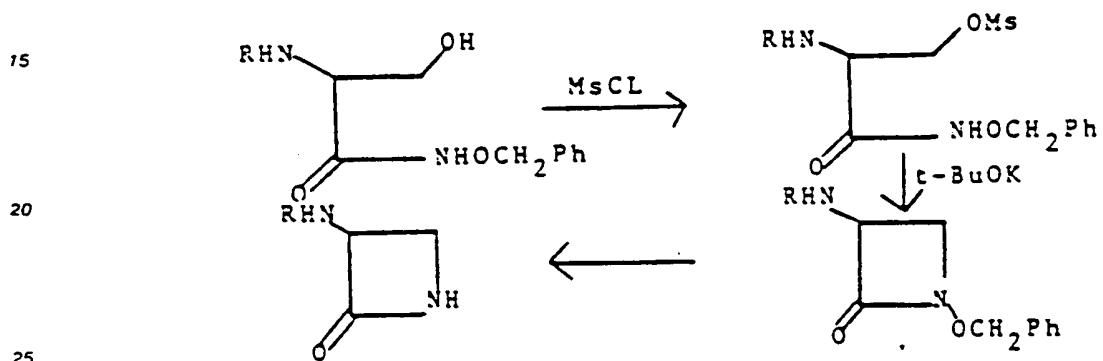
Scheme (d)

as illustrated by Examples 2-3.

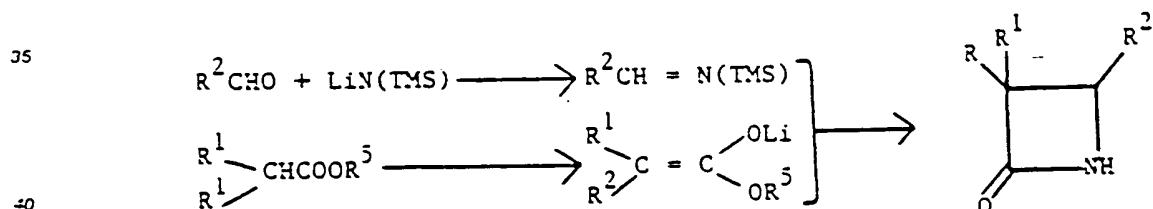
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Scheme (e)

10 as taught by M. A. Krook and M. J. Miller (J. Org. Chem., 1985, 50, 1126-1128), the following type of compounds can be prepared.

Scheme (f)

30 as taught by Hart, D. J. et al. (J. Org. Chem., 48, pp. 289-294, 1983); the following class of compounds can be prepared.



wherein R^5 is as previously defined; and
TMS is trimethylsilyl.

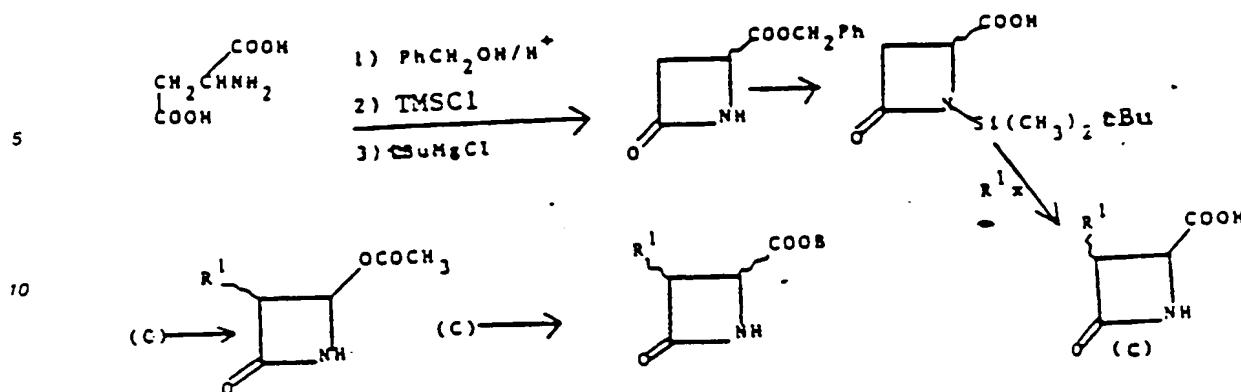
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Scheme (g)

as taught by P. J. Reider and E. J. J. Grabowski (Tet. Lett., 23, p. 2293, 1982); the following groups of compounds can be prepared.

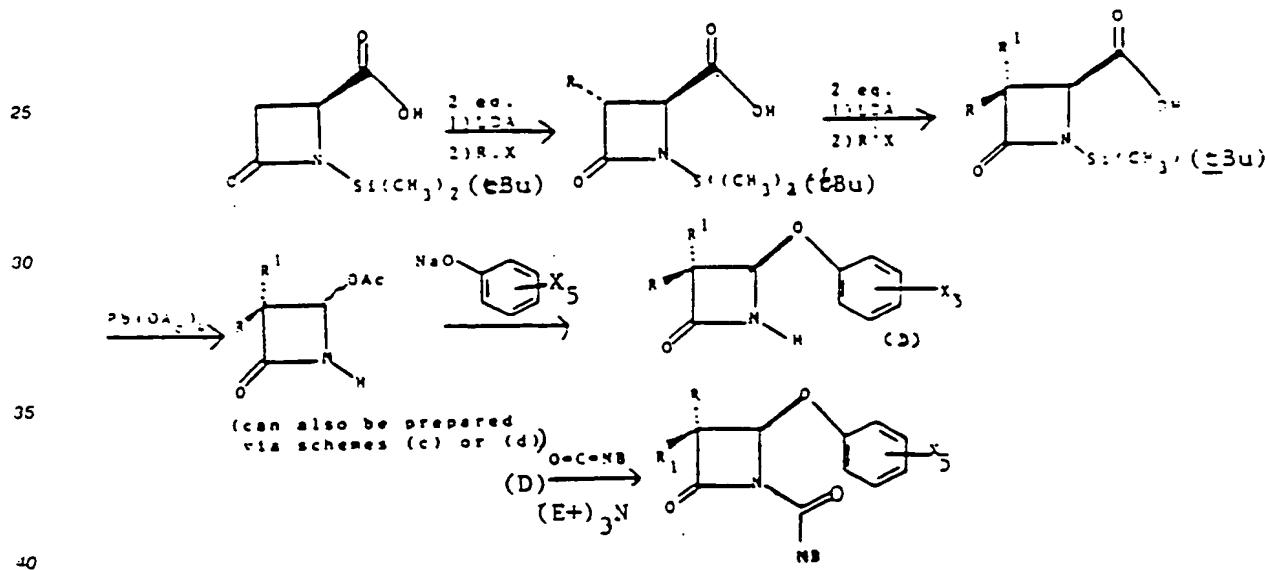
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Scheme (h)

20 as illustrated by Examples 20 and 21:



This invention also relates to a method of treating inflammation in patients using a compound of Formula (I), particularly a preferred compound as the active constituent.

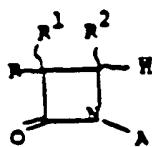
45 It has been found that the compounds of Formula (I) are effective inhibitors of the proteolytic function of human granulocyte elastase as shown below:

50

55

TABLE I

5



10

15	R	R ¹	R ²	A	I _{D₅₀} (μg/ml)	K _i (μM)	k _{obs} /I (M ⁻¹ sec ⁻¹)
20	H	H	SOCH ₃	COCH ₃	10.00		
	H	H	OCOCH ₃	COCH ₃	3.00		
	H	C ₂ H ₅	OCOCH ₃	H	15.00		
	H	C ₂ H ₅	OCOCH ₃	COCH ₃	0.10	0.36	15100
25	H	n-propyl	OCOCH ₃	COCH ₃	0.01		
	H	C ₆ H ₅ (trans)	COOC ₂ H ₅	H	10.00		
	H	H	COOCH ₂ C ₆ H ₅	SO ₂ (p-C ₆ H ₄ -NO ₂)	3.00		
30	CH ₃	CH ₃	OCOCH ₃	COCH ₃	0.50		
	H	C ₆ H ₅ (trans)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₄ -NO ₂)	4.00		
	H	C ₆ H ₅ (cis)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₄ -NO ₂)	3.00		
	H	CH ₃ O	COOCH ₂ C ₆ H ₅	COCH ₃	2.00		
35	H	n-propyl	OCOCH ₃	SO ₃ ⁻ (Bu) ₄ ⁺	8.00		
	H	C ₂ H ₃ (cis)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₄ -NO ₂)	0.02		
	H	C ₂ H ₅ (cis)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₄ -NO ₂)	0.05		3925
40	H	C ₂ H ₅ (trans)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₄ -NO ₂)	0.05		39300
	H	C ₂ H ₅ (trans)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₄ -CH ₃)	0.01		
	H	n-propyl (trans)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₄ -NO ₂)	0.06		
45	H	CH ₃ CHCH (cis)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₄ -NO ₂)	0.05		
	H	CH ₂ CH	p-(C ₆ H ₄ -NO ₂)	H	1.50		
	H	C ₂ H ₅	OCOCH ₂ CH ₂ COOH	COCH ₃	2.00	4514	
50	H	C ₂ H ₅ (trans)	OCOPh	COCH ₃	0.19	81000	

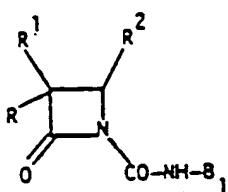
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TABLE I (Continued)

S	R	R ¹	R ²	A	ID ₅₀ (μg/ml)	Ki (μM)	k _{obs} /I (M ⁻¹ sec ⁻¹)
10	H	C ₂ H ₅ (cis)	OCOPh	COCH ₃	-	0.21	28500
	H	C ₂ H ₅	OCOCH ₃	COCH ₂ CH ₂ COOH	-	1.43	2250
	H	C ₂ H ₅ (cis)	OCOCH ₃	COPh	-	0.14	-
15	H	C ₂ H ₅ (trans)	OCOCH ₃	COPh	-	0.34	76600
	H	C ₂ H ₅ (trans)	OPh	COCH ₃	-	4.30	5270
	H	C ₂ H ₅ (trans)	OC ₂ H ₅	COCH ₃	-	11.90	1670
20	H	C ₂ H ₅ (trans)	OPh-p-COOH	COCH ₃	-	3.40	8727
	H	C ₂ H ₅ (trans)	OPh-p-COOH	COOC ₂ H ₅	-	2.10	8680
	H	C ₂ H ₅ (trans)	OPh-p-COOH	CONHCH ₃	-	16.50	-
25	H	C ₂ H ₅ (cis)	CON(CH ₂) ₄	SO ₂ (p-C ₆ H ₄ -CH ₃)	-	27.70	541
	H	C ₂ H ₅ (cis)	COOCH ₂ C ₆ H ₄ -p-COOH	SO ₂ (p-C ₆ H ₄ -CH ₃)	-	4.20	299
	H	C ₂ H ₅ (cis)	CON(CH ₃)CH ₂ COOH	SO ₂ (p-C ₆ H ₄ -CH ₃)	-	22.00	165
30	H	C ₂ H ₅ (trans)	OCH ₂ COOH	COOC ₂ H ₅	-	-	512
	H	C ₂ H ₅ (cis)	OCH ₂ COOH	COOC ₂ H ₅	-	-	796
	H	n-propyl (trans)	OCH ₂ COOH	COOC ₂ H ₅	-	-	1504
35	H	C ₂ H ₅ (trans)	OCH ₂ CONHCH ₂ COOH	COOC ₂ H ₅	-	-	1000
	H	C ₂ H ₅ (trans)	OCH(CH ₃)COOH	COOC ₂ H ₅	-	-	346
	H	C ₂ H ₅ (cis)	COOCH ₂ COOH	SO ₂ (p-C ₆ H ₄ -CH ₃)	-	-	1554

40 ID₅₀ is the effective dosage in micrograms per milliliter (μg/ml) for 50%
inhibition of the enzyme activity two minutes after time zero. Ki is the
concentration of the inhibitor (micromolar, μM) giving 50% of the control
45 enzyme activity. k_{obs}/I (M⁻¹ sec⁻¹) is the second order rate constant
of inactivation of the enzyme.

Table II



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	R	R ¹	R ²	R ₁	k _{25°C} /I
5	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	(CH ₂) ₄ Ph	10,894
	C ₂ H ₅	C ₂ H ₅	O-Ph	CH ₂ -(4-COOH-Ph)	1501
	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	CH ₂ -cyclohexyl	1424
	C ₂ H ₅	H	O-(4-COOH-Ph)	CH ₂ Ph ↗	4000
10	C ₂ H ₅	CH ₃	O-(4-COOH-Ph)	CH ₂ Ph	2000
	CH ₂ CH=CH ₂	H	O-(4-COOH-Ph)	CH ₂ Ph	5400
15	C ₃ H ₇	C ₂ H ₅	O-(4-COOH-Ph)	CH ₂ Ph	3290
20	cyclopentane		O-(4-COOH-Ph)	CH ₂ Ph	1900
	(R and R ¹ combined and form the cyclopentane ring)				
25	C ₂ H ₅	CH ₂ OCH ₃	O-(4-COOH-Ph)	CH ₂ Ph	1900
	C ₂ H ₅	CH ₃	O-(4-COOH-Ph)	CH ₂ CH(CH ₃)Ph	2553
	C ₂ H ₅	C ₃ H ₇	O-(4-COOH-Ph)	CH ₂ -(2-Naph)	51,000
	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	CH(CH ₃)-(1-Naph)	14,128
30	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	CH ₂ -(4-C1-Ph)	3419
	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	CH ₂ (4-CH ₃ -Ph)	3965
	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	CH ₂ (4-F-Ph)	2337
	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	CH ₂ (4-OCH ₃ -Ph)	5162
35	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	CH ₂ (4-NO ₂ -Ph)	5075
	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	CH(CH ₃)-(3-C1-4-cyclo- hexyl-Ph)	20,776
40	C ₂ H ₅	CH ₂ OCH ₃	O-(4-COOH-Ph)	CH ₂ -(3,4-methylene- dioxy-Ph)	16,984
45	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	CH ₂ -(2-benzofuran) ↗	13,151
	C ₂ H ₅	C ₂ H ₅	O-(2-(6-COOH-Naph))	CH ₂ Ph	5561
	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	CH ₂ (4-(4-C1-Ph)- SO ₂ NHCOPh)	1730

	R	R ¹	R ²	R ₁	k_{obs}/I
	C ₂ H ₅	C ₂ H ₅	O-(3-CO-NHCH ₂ -Ph) COOH	CH ₂ Ph	3047
5	C ₂ H ₅	C ₂ H ₅	O-(3-COOH-Ph)	CH ₂ Ph	1763
	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	CH ₂ -(4-PhO-Ph)	12.036
10	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	CH ₂ -(4-HN(CH ₃) ₂ -Ph) •CF ₃ COO ⁻	9983
	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	(CH ₂) ₄ OPh	3447
15	C ₂ H ₅	C ₂ H ₅	O-(4-COOH-Ph)	(CH ₂) ₄ CH(CH)Ph	4200
	C ₂ H ₅	C ₂ H ₅	O-(4-N(CH ₃) ₃ I ⁻ -Ph)	CH ₂ Ph	1700
20	C ₂ H ₅	C ₂ H ₅	-1-imidazolyl	CH ₂ Ph	200
25	C ₂ H ₅	C ₂ H ₅		CH ₂ Ph	2000
30	C ₂ H ₅	C ₂ H ₅		CH ₂ Ph	6300
35	C ₂ H ₅	C ₂ H ₅		CH ₂ Ph	2422
40	C ₂ H ₅	C ₂ H ₅		CH ₂ Ph	2422
45					
50					
55					

Table II
(continued)

	R	R ¹	R ²	k_{obs}/L	
5	C ₂ H ₅	H	O-(4-COOH-Ph)	Ph-4-COOH	13,563
	C ₃ H ₇	C ₃ H ₇	O-(4-COOH-Ph)	CH ₂ Ph	2,500
	allyl	C ₂ H ₅	O-(4-COOH-Ph)	CH ₂ Ph	1974
10	CH ₂ Ph	C ₂ H ₅	O-(4-COOH-Ph)	CH ₂ Ph	87
	C ₂ H ₅	CH ₂ OCH ₃	O-(4-COOH-Ph)	CH ₂ -2-Naph	50,000
	C ₂ H ₅	H	Ph-4-COOH	CH ₂ Ph	900
15	H	OMe	Ph-4-COOH	CH ₂ -2-Naph	1340
	C ₂ H ₅	C ₃ H ₇	O-(4-COOH-Ph)	CH ₂ Ph-3-CF ₃	55,000
	C ₂ H ₅	CH ₃	O-(4-COOH-Ph)	CH(Et)-5-benzofuryl	750,000
	C ₂ H ₅	CH ₃	O-(4-COOH-Ph)	CH(Et)-3-thienyl	78,800
20	C ₂ H ₅	CH ₂ OCH ₃	O-(4-COOH-Ph)	CH(nPr)Ph	75,000
	C ₂ H ₅	C ₃ H ₇	O-(4-COOH-Ph) CO(CH ₂) ₂ COOH-Ph	CH(Et)Ph	87,000
25	C ₂ H ₅	C ₃ H ₇	O-(4-CH ₂ COOH-Ph)	CH(Et)Ph	54,000
	C ₂ H ₅	CH ₃	O-(4-COOH-Ph)	Cyclopentyl	—
	C ₂ H ₅	CH ₃	O-(4-COOH-Ph)	CH(CH ₃)CH ₂ CH ₂ CH ₃	—
30	C ₂ H ₅	CH ₃	O-(4-CONH ₂ Ph)	CH ₂ Ph	12,500
	C ₂ H ₅	CH ₃	O-(4-COOH-Ph)	CH ₂ (3,5-diMe- 4-COOH-Ph)	5,500
35	C ₂ H ₅	CH ₃	O-(4-CONH ₂ Ph)	CH ₂ (3,5-diMe- 4-COOH-Ph)	30,000
	C ₂ H ₅	CH ₃	O-(4-COOH-Ph)	CH ₂ (3,4-diMeO-Ph)	11,300

40

Me represents CH₃

Ph represents phenyl

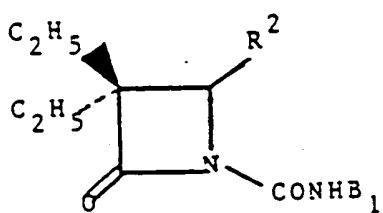
Pr represents propyl

Bu represents butyl

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Table III



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	R ²	¹ H	k _{obs} /I
	OCH ₂ COOH	CH ₂ Ph-4-Ph	2901
	O-(4-COOH-Ph)		4157
20	O-(allyl)	CH ₂ Ph-4-Ph	12,545
	-1-imidazolyl	CH ₂ Ph-4-Ph	461
	1-triazolyl	CH ₂ Ph-4-Ph	2144
25	(1-methyl-tetrazol-5-yl)thio	CH ₂ Ph	3658
	(1-H-triazol-3-yl)thio	CH ₂ Ph	116
	1-tetrazolyl	CH ₂ Ph	948
30	[2H-1-pyridonyl]	CH ₂ Ph	357
	O-Ph-4-CO NH ₂	CH ₂ -2-Naph(6-COOH)	40,650
	1-benzimidazolyl	CH ₂ Ph	69
35		CH ₂ Ph	351
	O-glyceryl	CH ₂ Ph	818
40	OCH ₂ CONH ₂	CH ₂ -Ph-4-Ph	51,802
	NH-COOMe	CH ₂ Ph	496
	OCH ₂ -COOH	CH-(Et)-Ph	5711
45	OCH ₂ -CONH ₂	CH-(Et)-Ph	102,974
	O-(4-COOH-Ph)	nBu	—
	O-(4-COOH-Ph)	cyclopentyl	—
	O-CH ₂ CON(Et) ₂	CH(Et)Ph	—

Table III
(Continued)

	<u>R²</u>	<u>R₁</u>	<u>k_{obs}/I</u>
5	O-(4-COOH-Ph)	CH ₂ Ph(2-OH)	1461
	O-(4-COOH-Ph)	CH ₂ Ph(4-tBu)	~ 21,774
	O-(4-COOH-Ph)	CH ₂ Ph(4-(3-COOH)Ph)	14,727
10	O-(4-COOH-Ph)	CH ₂ Ph(4-CO-N())O	2036
	O-(4-COOH-Ph)	CH ₂ Ph(4-CH ₂ Ph)	8032
	O-(4-COOH-Ph)	CH ₂ Ph(3-CH ₃)	6932
	O-(4-COOH-Ph)	CH ₂ Ph(3,4-(CH ₂) ₄)	62,883
	O-(4-COOH-Ph)	CH ₂ Ph(3,4-DiMe)	20,600
	O-(4-COOH-Ph)	CH ₂ Ph(4-i-Pr)	18,846
	O-(4-COOH-Ph)	CH ₂ Ph(4-S(O) ₂ Me)	3350
	O-(4-COOH-Ph)	CH ₂ Ph(4-COMe)	5916
	O-(4-COOH-Ph)	CH ₂ Ph(4-OMe-3-Me)	13,126
	O-(4-COOH-Ph)	CH ₂ Ph(4-OCH ₂ Ph)	12,036
15	O-(4-CH(COOH)NHAc-Ph)	CH ₂ Ph	1675
	O-(4-CH(OH)COOH-Ph)	CH ₂ Ph(3,4-DiMe)	17,526
	O-(3-OH-4-COOH-Ph)	CH ₂ Ph(4-Me)	9252
	O-(2-(CH ₂) ₃ NMe ₂ -Ph)	CH ₂ Ph	629
	O-(4-CH ₂ COOH-Ph)	CH ₂ Ph(4-Ph)	28,870
20	O-(4-COOH-Ph)	CH ₂ Ph(4-Cl)	10,000
	O-(4-COOH-Ph)	CH ₂ Ph(4-Br)	10,000
25	O-(4-COOH-Ph)	CH ₂ Ph(4-NO ₂)	10,000
	O-(4-COOH-Ph)	CH ₂ Ph(4-CN)	10,000
	O-(4-COOH-Ph)	CH ₂ Ph(4-CH ₃)	10,000
	O-(4-COOH-Ph)	CH ₂ Ph(4-CH ₂ Cl)	10,000
	O-(4-COOH-Ph)	CH ₂ Ph(4-CH ₂ Br)	10,000
30	O-(4-COOH-Ph)	CH ₂ Ph(4-CH ₂ NO ₂)	10,000
	O-(4-COOH-Ph)	CH ₂ Ph(4-CH ₂ CN)	10,000
	O-(4-COOH-Ph)	CH ₂ Ph(4-CH ₂ CH ₃)	10,000
	O-(4-COOH-Ph)	CH ₂ Ph(4-CH ₂ CH ₂ Cl)	10,000
	O-(4-COOH-Ph)	CH ₂ Ph(4-CH ₂ CH ₂ Br)	10,000
35	O-(4-COOH-Ph)	CH ₂ Ph(4-CH ₂ CH ₂ NO ₂)	10,000
	O-(4-COOH-Ph)	CH ₂ Ph(4-CH ₂ CH ₂ CN)	10,000
	O-(4-COOH-Ph)	CH ₂ Ph(4-CH ₂ CH ₂ CH ₃)	10,000
	O-(4-COOH-Ph)	CH ₂ Ph(4-CH ₂ CH ₂ CH ₂ Cl)	10,000
	O-(4-COOH-Ph)	CH ₂ Ph(4-CH ₂ CH ₂ CH ₂ Br)	10,000

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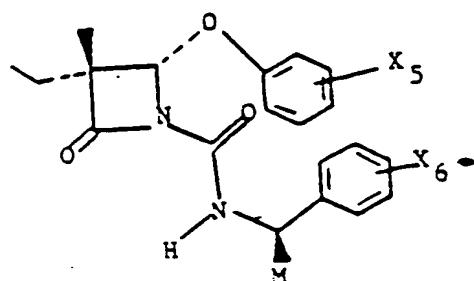
Table IV

5

10

	R	R¹	R²	S	k_{obs}/I
15	C_2H_5	$-CH_3$	$O-(4-COOH-Ph)$		4376
20	C_2H_5	H	$O-(4-COOH-Ph)$		10.066
25	C_3H_7	C_3H_7	$O-(4-COOH-Ph)$		1446 (lower ref.) 4324 (higher ref.)
30	C_2H_5	H	$O-(4-COOH-Ph)$	$-N(CH_2Ph)_2$	5977
35	C_2H_5	H	$O-(4-COOH-Ph)$	$-OCH_2-(4-COOC_2H_5-Ph)$	227.460
40	C_2H_5	C_2H_5	$O-(4-COOH-Ph)$	$-OCH_2-(4-COOC_2H_5-Ph)$	14.331
45	C_2H_5	H	$O-(4-COOH-Ph)$	$-N(C_2H_5)(CH_2Ph)$	82.956
50					
55					

Table V

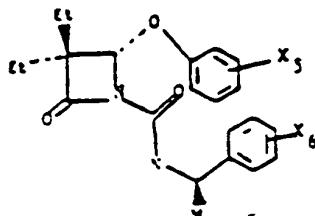


	X_5	M	X_6	k_{obs}/I
20	4-COOH	Et	H	92,000
	4-COOH	nPr	H	152,000
	4-COOH	CH_2OMe	H	6,094
25	$4-CH_2COOH$	Et	H	140,000
	4-COOH	Me	4-Me	47,000
	4-COOH	Et	4-Me	—
30	4-COOH	$PhCH_2$	H	25,000
	$4-CH_2COOH$	nPr	H	227,000
	4-COOH	nPr	CH_3	—
35	4-COOH	nPr	H	120,000
	4-COOH	Et	$3,4-(OCH_2O)$	—
	$4-CH_2COOH$	nBu	H	—
40	4-COOH	allyl	H	—
45				
50				
55				

Table VI

5

10



	X ₅	M	X ₆	k _{obs} /l
15	4-COOH	Me	H	4016
	4-COOH	Me	4-Ph	74,000
	4-CH ₂ COOH	Me	H	8,373
20	4-COOH	Me(s)	4-Ph	49246
	4-COOH	Ph	Ph	67754
	4-COOH	Me	4-(2'-Cl-Ph)	245130
25	4-COOH	Et	4-Ph	26382
	4-COOH	Et	H	76204
	4-COOH	Et	H	37084
30	4-CO-(CH ₂) ₂ -COOH	Me	H	272190
	4-CO-(CH ₂) ₂ COCH	Et	H	116060
	4-COOH	nPr	H	24,994
35	3,5-Me ₂ -4-COOH	Et	H	126,000
	4-CH ₂ COOH	Et	H	124560
	3-OH-4-COOH	Et	H	5885
40	3-CH ₂ COOH	Me	H	9101
	4-CH=CH-COOH	Me	H	6981
	4-COOH	CH ₂ OMe(S)	H	
45	4-CH ₂ COOH	CH ₂ OMe(S)	H	10680
	4-COOH	Me	-Me	4743
	4-COOH	iPr(S)	H	177075
50	4-COOH	iPr	H	188,000
	4-CH ₂ COOH	nPr	H	11004
	4-CH ₂ COOH	CH ₂ OMe(R)	H	
	3,5-Me ₂ -4-COOH	nPr	H	

55

Table VI
(Continued)

5

	X_5	H	X_6	k_{obs}/I
10	3-CH ₂ COOH	Et	4-Me	
	4-(CH ₂) ₂ COOH	Me	H	9481
	3-CH ₂ COOH	Et	H	81018
	4-COOH	CH ₂ OMe(R)	H	6981
15	4-COOH	Et	3-Me	
	4-CH ₂ COOH	Et	3-Me	
	4-CO(CH ₂) ₂ COOH	allyl	4-Me	
20	4-COOH	Me	4-Me	
	4-CH ₂ COOH	Et	3-Cl	
	4-COOH	Et	3-Cl	
25	4-COOH	allyl	3-Me	
	4-COOH	nPr	3-Me	
	4-CH ₂ COOH	allyl	4-Me	664,000
30	3-CH ₂ COOH	allyl	4-Me	
	4-CH ₂ COOH	allyl	3-Me	
	4-CH ₂ COOH	nPr	3-Me	
	4-CO(CH ₂) ₂ COOH	nPr	4-Me	
35	3-CH ₂ COOH	allyl	H	
	3-CH ₂ COOH	CH ₂ OMe(S)	H	
	4-COOH	allyl	H	
40	4-CH ₂ COOH	allyl	H	
	4-COOH	Et	4-Me	
	4-COOH	Et(S)	4-Me	
45	4-COOH	allyl	4-Me	
	4-COOH	nPr	4-Me	389,000
	3-CH ₂ COOH	nPr	4-Me	
	4-CH ₂ COOH	nPr	4-Me	557,000

50

55

Table VI
(Continued)

	X_5	M	X_6	λ_{obs} / I
5	3-CH ₂ COOH	Et	4-Cl	
10	4-COOH	Et	4-Cl	
15	4-CH ₂ COOH	Et	4-Me	
20	3-CH ₂ COOH	Et	3-Cl	
25	4-COOH	allyl	3,4-methylenedioxy	
30	4-COOH	nPr	3,4-methylenedioxy	605.000
35	4-CH ₂ COOH	allyl	3,4-methylenedioxy	867.000
40	4-CH ₂ COOH	nPr	3,4-methylenedioxy	
45	3-CH ₂ COOH	CH ₂ COOH	4-Me	
50	3-CH ₂ COOH	nPr	H	
55	4-COOH	Et	3,4-methylenedioxy	
60	4-CH ₂ COOH	Et	3,4-methylenedioxy	
65	4-COOH	Et	3,4-Me ₂	
70	4-COOH	CH ₂ C≡CCH ₃	H	
75	4-CH ₂ COOH	CH ₂ C≡CCH ₃	H	
80	4-COOH	nBu	H	
85	2-NO ₂ -4-CH ₂ COOH	Et	H	
90	4-COOH	Et	4-F	
95	4-COOH	Et	3-Me-4-OMe	

Protocol - Enzyme Assays for the Inhibition of Human Polymorphonuclear Leukocyte Elastase Via Hydrolysis of N-t-Boc-alanyl-alanyl-prolylalanine-p-nitroanilide (Boc-AAPAN) or N-t-Boc-alanyl-prolylvaline-p-nitroanilide (Boc-AAPVN) Reagent:

0.05M TES (N-tris[hydroxymethyl]methyl-2-amino-ethanesulfonic acid) Buffer, pH 7.5.

0.2 mM Boc-AAPAN or Boc-AAPVN.

To prepare substrate, the solid was first dissolved in 10.0 ml DMSO. Buffer at pH 7.5 was then added to a final volume of 100 ml.

Crude extract of human polymorphonuclear leukocytes (PMN) containing elastase activity.

Inhibitors (azetidinones) to be tested dissolved in DMSO just before use.

50

Assay Procedure:

To 1.0 ml of 0.2 mM Boc-AAPAN in a cuvette, 0.01-0.1 ml of DMSO with or without inhibitor was added. After mixing, a measurement was taken at 410 m μ to detect any spontaneous hydrolysis due to presence of test compound. 0.05 Milliliters of PMN extract was then added and the $\Delta OD/min$ at 410 m μ was measured and recorded. Beckman model 35 spectrophotometer was used.

Results:

Results in Table I were reported as ID₅₀, effective dosage in micrograms per milliliter ($\mu\text{g}/\text{ml}$) for 50% inhibition of the enzyme activity 2 minutes after zero time.

5 Results were also expressed as Ki, the micromolar concentration of the inhibitor (μM) giving 50% of the control enzyme activity; or as k_{obs/l} which is the second order rate constant in per mole per second for inactivation of the enzyme.

10 Comments:

The elastase activity in the crude PMN extract may vary from one preparation to another. A control of each new batch is run, and the volume added in the assay procedure is adjusted according to activity.

Accordingly, the compounds of Formula (I) can be used to reduce inflammation and relieve pain in 15 diseases such as emphysema, rheumatoid arthritis, osteoarthritis, gout, bronchial inflammation, atherosclerosis, sepsis, septicemia, shock, periodontitis, cystic fibrosis, infectious arthritis, rheumatic fever and the like.

For treatment of inflammation, fever or pain, the compounds of Formula (I) may be administered orally, 20 topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral 25 use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant 30 and palatable preparation. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, 35 stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient 40 is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium 45 carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadeca-ethylenoxygenol, or condensation products of ethylene oxide with partial 50 esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The said aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

55 Oily suspension may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable

oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

5 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

10 The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oils, or mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

15 Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile 20 injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In this addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty 25 acids such as oleic acid find use in the preparation of injectables.

25 The compounds of Formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

30 For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the anti-inflammatory agents are employed.

35 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 5 mg to 5 gm of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 25 mg to about 500 mg of active ingredient.

40 It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

EXAMPLE 1

45

1-p-nitrophenylsulfonyl-4-benzyloxycarbonyl azetidin-2-one

50 Diazabicycloundecane (152 mg, 1 mM) was added to a mixture of 205 mg (1 mM) 4-benzyloxycarbonyl azetidin-2-one and 181 mg (1 mM) p-nitrobenzenesulfonyl chloride in 10 ml methylene chloride at room temperature. After stirring 2-1/2 hours, the orange solution was washed with water, dried over MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel in hexane/ethyl acetate to yield 64 mg (17%) of 1-p-nitrophenylsulfonyl-4-benzyloxycarbonyl azetidin-2-one.

55 NMR (CDCl₃): δ 3.3 (2H, doublet-quartet), 4.8 (q, 1H), 5.2 (s, 2H), 7.2 (s, 5H), 8.2 (m, 4H).

EXAMPLE 2

1-Acetyl-3,3-dimethyl-4-acetoxyazetidin-2-one

5

Step A: Preparation of 2-methyl-prop-1-enylacetate

A mixture of 72 g (1 M) isobutyraldehyde, 153 g (1.5 M) acetic anhydride and 12 g (0.125 M) potassium acetate was refluxed seven hours. The cooled reaction mixture was washed with water and stirred with 300 ml saturated NaHCO_3 at 0° C for 45 minutes. The organic phase was dried over K_2CO_3 to yield a yellow oil which was distilled at atmospheric pressure to give 35.41 g (31%) of 2-methyl-prop-1-enylacetate, b.p. 122-126°.

NMR (CDCl_3): δ 1.6 (s, 6H), 2.1 (s, 3H), 6.9 (milt. 1H).

15

Step B: Preparation of 3,3-dimethyl-4-acetoxyazetidin-2-one

Chlorosulfonyl isocyanate (16 ml) was added to a solution of 22.8 g (0.2 M) 2-methyl prop-1-enyl acetate in 50 ml methylene chloride at 0° under nitrogen. After stirring at 0° for 20 hours, the reaction mixture was added to a mixture of 20 ml water, 90 g ice, 48 g NaHCO_3 and 16.6 g Na_2SO_3 and stirred at 0° for 30 minutes. This was then extracted with 300 ml CH_2Cl_2 and the organic phase washed with brine, dried over MgSO_4 and concentrated in vacuo to give 27.75 g oil which was chromatographed on silica gel in hexane:ethyl acetate to yield 2.17 g (8.5%) of 3,3-dimethyl-4-acetoxyazetidin-2-one.

25 NMR (CDCl_3): δ 1.2 (s, 3H), 1.3 (s, 3H), 2.2 (s, 3H), 5.6 (s, 1H).

Step C: Preparation of 1-acetyl-3,3-dimethyl-4-acetoxyazetidin-2-one

30 A mixture of 283.3 mg (1.8 mM) 3,3-dimethyl-4-acetoxyazetidin-2-one, 2 ml pyridine and 2 ml acetic anhydride was heated to 100° in a sealed tube for 36 hours. The reaction mixture was concentrated in vacuo and the residue chromatographed on silica gel in hexane:ethyl acetate to yield 295 mg (82%) of 1-acetyl-3,3-dimethyl-4-acetoxyazetidin-2-one.

NMR (CDCl_3): δ 1.2 (s, 3H), 2.2 (s, 3H), 2.5 (s, 3H), 6.1 (s, 1H).

35

EXAMPLE 3

40

1-Acetyl-4-acetoxy-3-n-propylazetidin-2-oneStep A: Preparation of Pent-1-enyl acetate

45

A mixture of 86 g (1M) valeraldehyde, 153 g (1.5 M) acetic anhydride, and 12 g (0.125 M) potassium acetate, was refluxed for 8 hours. The cooled mixture was then stirred with 100 ml saturated aqueous NaHCO_3 for one hour. The organic phase is separated, dried over K_2CO_3 , and distilled at 40 mm to yield 46.15 g (45%) of pent-1-enylacetate, b.p. 89° C.

50 NMR (CDCl_3): δ 1.0 (tr, 3H), 1.2-2.0 (milt., 4H), 2.1 (s, 3H), 4.7-5.6 (milt. 1H), 7.0-7.3 (milt., 1H).

Step B: Preparation of 4-acetoxy-3-n-propylazetidin-2-one

55 Eight hundred microliters of chlorosulfonyl isocyanate was added to a solution of 1.28 g (10 mM) pent-1-enyl acetate in 5 ml methylene chloride at 0° under nitrogen. After stirring at 0° 5 days, the reaction mixture was added dropwise to a mixture of 5 g ice, 1.15 ml water, 2.82 g NaHCO_3 and 1.0 g Na_2SO_3 and stirred at 0° for 30 minutes. The mixture was extracted with 2 X 25 ml methylene chloride and the

combined organic phases washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel in hexane/ethyl acetate to yield 60 mg trans 4-acetoxy-3-n-propylazetidin-2-one (3.4%).

NMR ($CDCl_3$): δ 1.0 (milt., 3H), 1.7 (milt., 4H), 2.2 (s, 3H), 3.2 (tr, 1H), 5.6 (s, 1H), 6.7 (lrs, 1H).

5

Step C: Preparation of 1-acetyl-4-acetoxy-3-n-propylazeticin-2-one

A mixture of 56 mg (0.33 mM) 4-acetoxy-3-propylazetidin-2-one, 1 ml acetic anhydride and 1 ml pyridine was stirred at 100° in a sealed tube for 24 hours. After concentrating in vacuo the residue was chromatographed on silica gel in hexane/ethyl acetate, to yield 16 mg (23%) 1-acetyl-4-acetoxy-3-n-propylazetidine-2-one.

NMR ($CDCl_3$): δ 1.0 (br tr, 3H), 1.7 (milt., 4H), 2.2 (s, 3H), 2.4 (s, 3H), 3.2 (tr, 1H), 6.1 (d, 1H).

15

EXAMPLE 4

20 1-Acetyl-4-methylsulfonylazetidin-2-one

Step A: Preparation of 1-acetyl-4-methylthioazetidin-2-one

25 A mixture of 300 mg (2.6 mM) 4-methylthioazetidin-2-one, 10 ml acetic anhydride and 10 ml pyridine was stirred at 100° in a sealed tube 24 hours. After concentrating in vacuo, the residue was chromatographed on silica gel in hexane/ethyl acetate to yield 324 mg (78%) of 1-acetyl-4-methylthioazetidine-2-one. NMR ($CDCl_3$): δ 2.4 (s, 3H), 2.41 (s, 3H), 3.2 (doublet-quartet, 2H), 5.1 (couplet-doublet, 1H).

30

Step B: Preparation of N-acetyl-4-methylsulfinylazetidin-2-one

35 A mixture of 130 mg (0.82 mM) N-acetyl-4-methylthioazetidinone and 200 mg (0.93 nM) 80% m-chloroperbenzoic acid in 5 ml methylene chloride was stirred at room temperature 5 minutes. After removing the solvent in vacuo. The residue was chromatographed on 2-2000 μ -silica gel plates in hexane/ethyl acetate to yield 57 mg (40%) of 1-acetyl-4-methylsulfinylazetidine-2-one. NMR ($CDCl_3$): δ 2.4 (s, 3H), 2.6 (s, 3H), 3.5 (milt., 2H), 4.9 (milt., 1H).

40

EXAMPLE 5

3-Azido-4-carboethoxy-1-(p-methoxyphenyl)azetidin-2-one

45

To a solution of 3.06 g of azidoacetyl chloride in 50 ml of CH_2Cl_2 was added dropwise a solution of 3.57 ml of triethylamine and 5.3 g of the imine formed from ethylglyoxalate and p-anisidine in 50 ml CH_2Cl_2 , with cooling at such a rate that the reaction temperature remained below 5°. The reaction was then stirred at room temperature for three hours and then washed sequentially with 1N HCl, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The organic phase was dried over magnesium sulfate, filtered, and evaporated, and the crude residue was recrystallized from carbon tetrachloride/hexane to afford 3.7 g. of 3-azido-4-carboethoxy-1-(p-methoxyphenyl)azetidine-2-one; m.p. 80-85°. NMR ($CDCl_3$): δ 7.2 (d, J = 9, 2H), 6.75 (d, J = 9, 2H), 4.9 (d, J = 6, 1H), 4.6 (d, J = 6, 1H), 4.25 (q, J = 8, 2H), 3.7 (s, 3H), 1.25 (t, J = 8, 3H).

55

EXAMPLE 6

4-Carboethoxy-3-chloro-1-(p-methoxyphenyl)azetidine-2-one

4-carboethoxy-3-chloro-1-(p-methoxyphenyl)azetidine-2-one was prepared by following the same procedure as described in Example 5 but using chloroacetyl chloride and the imine formed from ethylglyoxalate and p-anisidine as the starting material. The crude product was recrystallized from ether (hexane) to give 5 3.1 g of 4-carboethoxy-3-chloro-1-(p-methoxyphenyl)azetidine-2-one, m.p. 99-100. NMR (CDCl_3): δ 7.2 (d, $J = 9$, 2H), 6.8 (d, $J = 9$, 2H), 5.1 (d, $J = 6$, 1H), 4.7 (d, $J = 6$, 1H), 4.25 (q, $J = 7$, 2H), 3.7 (s, 3H), 1.25 (t, $J = 7$, 3H).

10

EXAMPLE 715 4-Carboethoxy-3-methoxy-1-(p-methoxyphenyl)azetidine-2-one

4-Carboethoxy-3-methoxy-1-(p-methoxyphenyl)azetidine-2-one was prepared by following the same procedure as described in Example 5 but using methoxyacetyl chloride as the starting material. After chromatography the compound crystallized as a white solid; m.p. 116-118. 20 NMR (CDCl_3): δ 7.2 (d, $J = 9$, 2H), 6.75 (d, $J = 9$, 2H), 4.7 (d, $J = 5$, 1H), 4.6 (d, $J = 5$, 1H), 4.2 (q, $J = 5$, 2H), 3.7 (s, 3H), 3.5 (s, 3H), 1.2 (t, $J = 5$, 3H).

25

EXAMPLE 84-Carboethoxy-1-(p-methoxyphenyl)-3-phenylazetidin-2-one

To a solution of 17 ml of triethylamine and 5.0 g of the imine formed from ethyl glyoxalate and p-anisidine in 100 ml of refluxing 1,2-dichloroethane was added dropwise over 2 hours a solution of 16 ml of freshly distilled phenylacetyl chloride in 50 ml of dichloroethane. After refluxing for three hours the reaction was worked-up as per the 3-azidoazetidinone. The crude residue was chromatographed to yield the cis and trans isomers of 4-carboethoxy-1-(p-methoxyphenyl)-3-phenylazetidin-2-one as oils; cis: NMR (CDCl_3): δ 7.2 (m, 7H), 6.7 (d, $J = 9$, 2H), 4.7 (s, 2H), 3.6 (s, 3H), 3.6 (q, $J = 7$, 2H), 0.7 (t, $J = 7$, 3H); trans: NMR (CDCl_3): δ 7.3 (m, 7H), 6.8 (d, $J = 9$, 2H), 4.5 (d, $J = 2$, 1H), 4.45 (d, $J = 2$, 1H), 4.1 (q, $J = 7$, 2H), 3.6 (s, 3H), 1.2 (t, $J = 7$, 3H).

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EXAMPLE 94-Carboethoxy-1-(p-methoxyphenyl)-3-vinylazetidin-2-one

45 4-Carboethoxy-1-(p-methoxyphenyl)-3-vinylazetidin-2-one was prepared by following the same procedure as described in Example 8 but using crotonyl chloride as the reagent. After chromatography the cis and trans isomers of the compound were obtained; cis (m.p. 70-72°), NMR (CDCl_3): δ 7.2 (d, $J = 9$, 2H), 6.8 (d, $J = 9$, 2H), 5.2-5.8 (m, 3H), 4.6 (d, $J = 6$, 1H), 4.2 (m, 3H), 3.7 (s, 3H), 1.2 (t, $J = 7$, 3H); trans (m.p. 50 72°), NMR (CDCl_3): δ 7.25 (d, $J = 9$, 2H), 6.8 (d, $J = 9$, 2H), 5.7-6.2 (m, 1H), 5.2-5.5 (m, 2H), 4.25 (br.s., 1H), 4.2 (q, $J = 7$, 2H), 3.9 (dd, $J = 1$, $J_2 = 6$, 1H), 3.75 (s, 1H), 1.25 (t, $J = 7$, 3H).

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EXAMPLE 104-Carboethoxy-3-ethyl-1-(p-methoxyphenyl)azetidin-2-one

The cis and trans isomers of 4-carboethoxy-3-vinyl-1-(p-methoxyphenyl)azetidine-2-one are each hydrogenated with palladium on carbon in ethanol to yield the corresponding cis and trans isomers of 4-carboethoxy-3-ethyl-1-(p-methoxy-phenyl)azetidine-2-one.

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EXAMPLE 1110 4-Carboethoxy-1-(p-methoxyphenyl)-3-(N-methyl-trifluoroacetamido)azetidin-2-one

A solution of 2.16 g of 3-azido-4-carboethoxy-1-(p-methoxyphenyl)-azetidine-2-one in ethanol was hydrogenated with palladium to yield 4-carboethoxy-1-(p-methoxyphenyl)-3-aminoazetidin-2-one. This amine was acylated with 1.1 ml of trifluoro acetic anhydride in 10 ml CH_2Cl_2 containing 1.5 ml pyridine, followed by methylation using 1 ml dimethyl sulfate in 30 ml acetone containing 3 g potassium carbonate. After isolation, the crude product was crystallized to give 2.2 g of 4-carboethoxy-1-(p-methoxyphenyl)-3-(N-methyltrifluoroacetamido)azetidine-2-one, m.p. 102-104°.
 NMR (CDCl_3): δ 7.2 (d, $J = 9$, 2H), 6.75 (d, $J = 9$, 2H), 5.5 (d, $J = 6$, 1H), 4.7 (d, $J = 6$, 1H), 4.2 (q, $J = 7$, 2H), 3.7 (s, 3H), 3.2 (br.s., 3H), 1.2 (t, $J = 7$, 3H).

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EXAMPLE 12

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4-Carboethoxy-3-methoxyazetidin-2-one

To a solution of 1.4 g of 4-carboethoxy-3-methoxy-1-(p-methoxyphenyl)azetidine-2-one in 50 ml acetonitrile at 0° was added a solution of 8.23 g of ceric ammonium nitrate in 50 ml H_2O over 3 minutes. After stirring at 0° for 1 hour the solution was poured into 200 ml of 10% sodium sulfite and extracted with 3 X 75 ml of ethyl acetate. The combined organic extracts were washed with 10% sodium sulfite and saturated sodium chloride solutions and dried over sodium sulfate. Filtration and evaporation gave an amber oil which was recrystallized from methylene chloride/hexane to give 700 mg of 4-carboethoxy-3-methoxyazetidine-2-one; m.p. 91-92°.
 NMR (CDCl_3): δ 7.1 (br.s., 1H), 4.7 (dd, $J_1 = 2$, $J_2 = 5$, 1H), 4.3 (d, $J = 5$, 1H), 4.15 (q, $J = 7$, 2H), 3.4 (s, 3H), 1.25 (t, $J = 7$, 3H).

Following substantially the same procedure as described in Example 12 but using an appropriate 3-substituted azetidinone compounds (a) - (f) were prepared:

(a) 4-Carboethoxy-3-chloroazetidin-2-one

NMR (CDCl_3): δ 7.3 (br.s., 1H), 5.0 (dd, $J_1 = 2$, $J_2 = 6$, 1H), 4.4 (d, $J = 6$, 1H), 4.2 (q, $J = 7$, 2H), 1.3 (t, $J = 7$, 3H).

(b) 4-Carboethoxy-3-phenylazetidin-2-one-2-(cis and trans)

NMR (CDCl_3): cis: δ 7.2 (s, 5H), 6.4 (br.s., 1H), 4.7 (d, $J = 6$, 1H), 4.4 (d, $J = 6$, 1H), 3.7 (q, $J = 7$, 2H), 0.75 (t, $J = 7$, 3H); trans: δ 7.2 (s, 5H), 6.9 (br.s., 1H), 4.3 (br.d, $J = 2$, 1H), 4.1 (q, $J = 7$, 2H), 4.0 (d, $J = 2$, 1H), 1.2 (t, $J = 7$, 3H).

(c) 4-Carboethoxy-3-(N-methyltrifluoroacetamido) azetidin-2-one

NMR (CDCl_3): δ 7.2 (br.s., 1H), 5.4 (d, $J = 6$, 1H), 4.5 (d, $J = 6$, 1H), 4.15 (q, $J = 7$, 2H), 3.2 (s, 3H), 1.2 (t, $J = 7$, 3H).

(d) 4-Carboethoxy-3-vinylazetidin-2-one(cis and trans)

NMR (CDCl_3): cis: δ 7.1 (br.s., 1H), 5.2-5.8 (m, 3H), 4.0-4.4 (m, 4H), 1.25 (t, $J = 7$, 3H); trans: δ 7.25 (br.s., 1H), 5.0-6.2 (m, 3H), 4.1 (q, $J = 7$, 2H), 3.9 (d, $J = 2$, 1H), 3.7 (dd, $J_1 = 2$, $J_2 = 7$, 1H), 1.2 (t, $J = 7$, 3H).

(e) 4-Carboethoxy-3-ethylazetidin-2-one

Cis: NMR(CDCl_3): δ 6.9 (br. s., 1H); 4.2 (m, 3H); 3.4 (dd, $J_1 = 6$, $J_2 = 8$, 1H); 1.51 (q, $J = 8$, 2H); 1.2 (t, $J = 7$, 3H); 1.0 (t, $J = 8$, 3H).
 Trans: NMR(CDCl_3): δ 6.8 (br. s., 1H); 4.2 (q, $J = 7$, 2H); 3.8 (d, $J = 2$, 1H); 3.2 (dd, $J_1 = 2$, $J_2 = 7$, 1H); 1.8 (-dq, $J_1 = 2$, $J_2 = 8$, 2H); 1.2 (t, $J = 7$, 3H); 1.0 (t, $J = 8$, 3H).

(f) 3-Azido-4-carboethoxyazetidin-2-one

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EXAMPLE 134-Carboethoxy-3-(N-methyltrifluoroacetamido)azetidine-2-one-1-sulfonic acid tetrabutylammonium salt

To a solution of 140 mg of 4-carboethoxy-3-(N-methyltrifluoroacetamido)azetidine-2-one in 5 ml of pyridine at 80° was added 250 mg of sulfur trioxide pyridine complex, and the resulting mixture was stirred for 30 minutes at 80°. The solution was poured into 100 ml of 0.5 N KH_2PO_4 and extracted with 2 X 25 ml of methylene chloride. The combined organic washes were back-extracted with 25 ml of KH_2PO_4 solution.

The combined aqueous phases were then treated with 680 mg of tetrabutylammonium hydrogen sulfate and extracted with 3 X 50 ml of methylene chloride. After drying (sodium sulfate) and evaporation of the organic phase the crude 4-carboethoxy-3-(N-methyltrifluoroacetamido)azetidine-2-one-1-sulfonic acid tetrabutylammonium salt was chromatographed to yield an oil.

NMR (CDCl_3): δ 5.3 (d, J = 6, 1H), 4.7 (d, J = 6, 1H), 4.15 (q, J = 7, 2H), 3.2 (m, 11H), 0.8-1.8 (m, 31H). Applying the same procedure as described above, the following tetrabutylammonium salts of other azetidine derivatives were prepared:

(a) 4-Carboethoxy-3-methoxyazetidin-2-one-1-sulfonic acid tetrabutylammonium salt

NMR (CDCl_3): δ 4.55 (d, J = 6, 1H), 4.5 (d, J = 6, 1H), 4.1 (q, J = 7, 2H), 3.4 (s, 3H), 3.2 (m, 8H), 0.8-1.8 (m, 31H).

(b) 4-Carboethoxy-3-vinyiazetidin-2-one-1-sulfonic acid tetrabutylammonium saltEXAMPLE 14

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4-Carboethoxy-1-(p-nitrobenzenesulfonyl)-3-phenylazetidin-2-one

To a solution of 720 mg of 4-carboethoxy-3-trans-phenylazetidin-2-one in 20 ml methylene chloride at 0° were added sequentially 595 mg of p-nitrobenzenesulfonyl chloride and 0.48 ml of DBU. The solution was stirred for several hours, diluted with 50 ml of methylene chloride, washed once with water and dried over sodium sulfate. Filtration and evaporation gave a crude residue which was chromatographed to yield pure 4-carboethoxy-1-(p-nitrobenzenesulfonyl)-3-phenyl-azetidin-2-one.

NMR (CDCl_3): δ 8.3 (d, J = 9, 2H), 8.2 (d, J = 9, 2H), 7.2 (br.s., 5H), 4.0 (q, J = 7, 2H), 3.7 (m, 2H), 1.2 (t, J = 7, 3H). Similarly prepared was the corresponding cis-3-phenyl compound. NMR (CDCl_3): δ 8.4 (d, J = 9, 2H), 8.25 (d, J = 9, 2H), 7.2 (s, 5H), 5.0 (s, 1H), 3.7 (m, 3H), 0.85 (t, J = 7, 3H).

Following the same procedure as described above but using appropriate reagents, the following compounds were prepared:

(a) 4-Carboethoxy-1-(p-nitrobenzenesulfonyl)-3-vinyiazetidin-2-one

NMR (CDCl_3): cis: δ 8.3 (d, J = 9, 2H), 8.2 (d, J = 9, 2H), 5.2-6.0 (m, 3H), 4.0-4.6 (m, 4H), 1.2 (t, J = 7, 3H); trans: δ 8.2 (d, J = 9, 2H), 8.15 (d, J = 9, 2H), 5.2-6.0 (m, 3H), 3.9-4.4 (m, 4H), 1.25 (t, J = 7, 3H).

(b) 4-Carboethoxy-3-ethyl-1-(p-nitrobenzenesulfonyl)azetidin-2-one(c) 3-Azido-4-carboethoxy-1-(p-nitrobenzenesulfonyl) azetidin-2-one(d) 4-Carboethoxy-3-chloro-1-(p-nitrobenzenesulfonyl)azetidin-2-oneEXAMPLE 15

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4-Carboethoxy-3-phenyl-1-trifluoromethanesulfonylazetidin-2-one

To a mixture of 1.2 g of 4-carboethoxy-3-phenylazetidin-2-one and 1.2 ml of triethylamine in 25 ml of methylene chloride at 0° was added dropwise over 10 minutes 11.25 ml of a 10% solution of trifluoromethanesulfenyl chloride in ether. After stirring for several hours the solution was washed with water, dried over sodium sulfate, filtered and evaporated. The crude residue was chromatographed to yield pure 4-carboethoxy-3-phenyl-1-trifluoromethanesulfenylazetidin-2-one as an oil.

NMR (CDCl_3): δ 7.2 (s, 5H), 4.6 (d, J = 3, 1H), 4.3 (m, 3H), 1.3 (t, J = 7, 3H).

EXAMPLE 16

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1-Tosyloxymethyl-3-n-Propyl-4-p-nitrophenylthioazetidin-2-one

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Step A: Preparation of 3-Propyl-4-p-nitrophenylthio azetidin-2-one

3-Propyl-4-acetoxy azetidinone, 171 mg, is refluxed with 200 mg p-nitrophenyl thiol in 10 ml benzene for 6 hours. The solution is washed 3x with aqueous Na_2CO_3 , dried with MgSO_4 , filtered and evaporated. The residue is chromatographed on silica gel, eluting with 10:1 CHCl_3 -EtOAc, affording 3-Propyl-4-p-nitrophenylthioazetidin-2-one.

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Step B: Preparation of 1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenylthio azetidin-2-one

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3-Propyl-4-p-nitrophenylthioazetidin-2-one, 266 mg, is stirred overnight at room temperature with 0.25 ml aqueous formalin (37%) and 17 mg K_2CO_3 . Water and formaldehyde are removed in vacuo, and flushed with 2 ml pyridine. The residue is taken up in 4 ml pyridine and treated for 1 hour at room temperature with 200 mg p-toluenesulfonyl chloride. The pyridine is evaporated and replaced with 5 ml benzene. The solution is washed with aqueous H_3PO_4 and then aqueous K_2HPO_4 , dried with MgSO_4 , filtered and evaporated. The residue is chromatographed on silica gel, eluting with 25:1 CHCl_3 -EtOAc, providing 1-tosyloxymethyl-3-n-propyl-4-p-nitrophenylthio-azetidin-2-one.

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EXAMPLE 17

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1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenylsulfinyl azetidin-2-one

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1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenylsulfinylazetidin-2-one, 450 mg, is treated for 1.2 hour in 10 ml CH_2Cl_2 with 172 mg m-chloroperbenzoic acid. The solution is washed with aqueous K_2HPO_4 , dried with MgSO_4 , filtered and evaporated, leaving pure 1-tosyloxymethyl-3-n-propyl-4-p-nitrophenylsulfinyl azetidin-2-one.

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EXAMPLE 18

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1-Acetoxyethyl-4-p-nitrophenylsulfinyl-3-n-propylazetidin-2-one

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Step A: Preparation of 3-n-propyl-4-p-nitrophenylthioazetidin-2-one

3-n-Propyl-4-acetoxy azetidinone (1.164 g, 6.58 mmole) and 1.02 g (6.58 mmole) p-nitrothiophenol were heated in a tube in the steam bath for 3.5 hours. The reaction mixture was cooled, diluted with 100 ml ethyl acetate, and the organic phase was washed with 100 ml water, 70 ml 1M H_3PO_4 and 3x100 ml saturated

K_2CO_3 . The organic phase was dried over magnesium sulfate, filtered, and solvent removed in vacuo to yield 1.53 g of yellow crystals which were chromatographed on a silica gel column in chloroform-ethyl acetate (4:1) to give 359 mg (19%) of 3-n-propyl-4-p-nitrophenylthioazetidin-2-one.
 NMR ($CDCl_3$): δ 0.92 (tr, 3H), 1.2-1.6 (br m, 4H), 3.10 (tr, 1H), 4.91 (c, 1H), 7.0 (br s, 1H), 7.50 (d, 2H), 8.20 (d, 2H).

5 Step B Preparation of 1-Acetoxyethyl-4-p-nitrophenylthio-3-n-propylazetidin-2-one

10 A mixture of 273 mg (0.94 mmole) azetidinone from Step A, 26.3 mg paraformaldehyde and 178 mg (0.56 mmole) cesium carbonate was stirred in 20 ml dry tetrahydrofuran at ambient temperature 16.5 hours under nitrogen. A mixture of 430 μ l pyridine and 2.56 ml acetic anhydride was added to the reaction mixture and the stirring continued 5 more hours. The solvents were removed in vacuo to give 604 mg crude product which was chromatographed on a silica gel flash column in hexane-ethyl acetate 3:1. This gave 102 mg (30%) of 1-acetoxyethyl-4-p-nitrophenylthio-3-n-propylazetidin-2-one.
 NMR ($CDCl_3$): δ 1.0 (tr, 3H), 1.2-1.85 (br m, 4H), 2.1 (s, 3H), 3.22 (tr, 1H), 4.95 (d, 1H), 5.18 (ABBA pattern, $J_1 = 30H_3$, $J_2 = 5H_3$, 2H), 7.65 (d, 2H), 8.22 (d, 2H).

20 Step C Preparation of 1-Acetoxyethyl-4-p-nitrophenylsulfinyl-3-n-propylazetidin-2-one

To a solution of 46 mg (0.127 mmole) azetidinone from Step B in 4 ml CH_2Cl_2 and 4 ml saturated aqueous $NaHCO_3$ was added 27 mg (0.127 mM) 80% m-chloroperbenzoic acid and the reaction mixture stirred vigorously 15 minutes. The phases were separated and the organic phase was dried over $MgSO_4$,
 25 filtered and stripped to yield 57 mg crude product which was chromatographed on a 1000 μ silica gel prep TLC plate in chloroform-ethyl acetate 4:1 to yield 15 mg (31%) of 1-acetoxyethyl-4-p-nitrophenylsulfinyl-3-n-propylazetidin-2-one.
 NMR ($CDCl_3$): δ 0.93 (tr, 3H), 1.2-1.8 (br m, 4H), 2.1 (s, 3H), 3.55 (tr, 1H), 4.66 (d, 1H), 5.04 (ABBA pattern, $J_1 = 34H_3$, $J_2 = 6H_3$, 2H), 8.2 (d, 2H), 8.52 (d, 2H).

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EXAMPLE 19

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4-Acetoxy-3-n-propylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt

A solution of 82 mg (0.463 mmole) 3-propyl-4-acetoxy azetidin-2-one in 5 ml pyridine was heated to 80°. 221 Mg (1.39 mmole) sulfur trioxide-pyridine complex was added and the reaction mixture stirred at 80° one hour. It was then poured into 100 ml 0.5M KH_2PO_4 (aqueous) and washed with 2x25 ml CH_2Cl_2 . The combined organic washes were backwashed with 25 ml 0.5M KH_2PO_4 . 157 Mg (0.463 mmole) Bu_4NHSO_4 was added to the combined aqueous phases. This was extracted with 2x25 ml CH_2Cl_2 and the combined extracts were dried over $MgSO_4$, filtered, and stripped in vacuo to yield 12.4 mg of an oily residue which was chromatographed on a small silica gel column, eluted first with 75 ml hexane/ethyl acetate (3:1) to remove starting material, then with 100 ml ethyl acetate:methanol (4:1) to yield 13 mg (5.7%) 4-acetoxy-3-n-propylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt.
 NMR ($CDCl_3$): δ 1.0 (m, 16H), 1.75 (br m, 20H), 2.16 (s, 3H), 2.90 (br s, H), 3.1 (tr, 1H), 3.3 (tr, 8H), 4.08 (br tr, 1H), 6.18 (s, 1H).

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EXAMPLE 20

55 (3R,4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carboxy)phenoxyazetidin-2-one

Step A: Preparation of (3R,4S)-1-t-butylidemethylsilyl-3-methylazetidin-2-one-4-carboxylic acid

To a solution of 27.5 ml of diisopropylamine in 150 ml of THF at -20°C was added 73.5 ml of 2.4N n-butyl lithium in hexane. After 15 minutes, the solution was cooled to -70°C and a solution of 20 gm of (4S)-1-t-butyldimethylsilylazetidin-2-one-4-carboxylic acid in 75 mL of THF was added. The solution was warmed to -20°C for 15 minutes before a solution of 13.5 mL of methyl iodide in 20 mL of THF was added. After 30 minutes at -20 to 0°C, the reaction was diluted with 300 mL of ether and then poured into a mixture of ice and 400 mL of 1N HCl. The layers were separated and the aqueous layer extracted with ether. The ether layers were washed with brine, dried over sodium sulfate and evaporated. The residue was crystallized from hexane to give 12-15 gms of (3R,4S)-1-t-butyldimethylsilyl-3-methylazetidin-2-one-4-carboxylic acid.

NMR (CDCl₃): δ .14 (2, 3H), .32 (s, 3H), .91 (d, 3H), .98 (s, 9H), 3.34 (dq, 1H), 3.71 (d, 1H)

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Step B: Preparation of (3R,4S)-1-t-butyldimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid

To a solution of 13 mL of diisopropylamine in 75 mL of THF at -20°C was added 35 mL of 2.4 M n-butyl lithium in hexane. After 15 minutes the solution was cooled to -70°C and a solution of 10 gms of (3R,4S)-1-t-butyldimethylsilyl-3-methylazetidin-2-one-4-carboxylic acid in 50 mL of THF was added. The solution was warmed to -20°C for 15 minutes and a solution of 6.7 mL of ethyl iodide in 10 mL of THF was added. After 30 minutes at -20 to 0°C the reaction was diluted with ether and poured into a mixture of ice and 1 N HCl. The layers were separated and the aqueous layer extracted with ether. The ether layers were each washed with brine, dried over sodium sulfate and evaporated. The residue was crystallized from a minimum amount of hexane to give 8.8 gms of (3R,4S)-1-t-butyldimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid.

NMR(CDCl₃): δ .15 (s, 3H), .31 (s, 3H), .98 (s, 9H), 1.04 (t, 3H), 1.22 (s, 3H), 1.78 (q, 2H), 3.94 (s, 1H).

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Step C: Preparation of (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one

To a solution of 13.0 gms of (3R, 4S)-1-t-butyldimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid in 75 mL of DMF and 15 mL of acetic acid under N₂ was added 23 gms of lead tetraacetate. The reaction was heated at 45-50°C for 18 hours and then poured into ice water and extracted into 2 portions of ether. The ether layers were washed with water, dilute sodium bicarbonate solution and brine, dried over sodium sulfate and evaporated to give 13 gm of crude oil containing a mixture of (3R, 4S) and (3R, 4R)-4-acetoxy-3-ethyl-3-methylazetidin-2-one. To this mixture in 50 mL of acetone was slowly added a solution of 14 gms of t-butyl 4-hydroxybenzoate in 50 mL of acetone, 5 mL of water and 29 mL of 2N sodium hydroxide. The reaction was stirred at room temperature for 64 hours and then diluted with water and extracted with 2 portions of ether. The ether layers were washed with brine, dried over sodium sulfate and evaporated. The residue was prep LC'ed with 15-25% ethylacetate:hexanes to give 6.3 gm of the higher R, (4R) ether and 1.5 gm of the desired (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one.

NMR (CDCl₃): δ 1.0 (t, 3H), 1.38 (s, 3H), 1.54 (s, 9H), 1.6-2.0 (m, 2H), 5.30 (s, 1H), 6.7 (brs, 1H), 6.78 (d, 2H), 7.90 (d, 2H).

Step D: Preparation of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one

To a solution of 1.5 gm of (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one in 25 mL of methylene chloride was added 1.2 mL of benzyl isocyanate, 1.4 mL of triethylamine and 10 mg of 4-dimethylaminopyridine. The reaction was stirred at room temperature for 16 hours and then evaporated. The residue was flash chromatographed eluting with 10 to 25% EtoAc Hexane to give 2.3 gm of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxy azetidin-2-one.

NMR (CDCl₃): δ .98 (t, 3H), 1.36 (s, 3H), 1.50 (s, 9H), 1.62 (m, 1H), 1.84 (m, 1H), 4.42 (d, 2H), 5.64 (s, 1H), 6.80 (brt, 1H), 7.06 (d, 2H), 7.24 (brs, 5H), 7.90 (d, 2H).

Step E: Preparation of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carboxy)phenoxyazetidin-2-one

To 2.3 gms of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy) phenoxyazetidin-

2-one in an ice bath under N₂ was added 5 mL of anisole and then 25 mL of precooled trifluoroacetic acid. After 1.5 hours at 0°C, the volatiles were removed *in vacuo* without heating and the residue flash chromatographed using hexane, then 15% EtoAc:Hexane, then 1% HoAc in 15% EtoAc:hexanes to give after ether trituration 1.8 gms of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carboxy)-5-phenoxyazetidin-2-one

NMR (CDCl₃): δ 1.03 (t, 3H), 1.46 (s, 3H), 1.66 (m, 1H), 1.94 (m, 1H), 4.50 (d, 2H), 5.76 (s, 1H), 6.9 (brt, 1H), 7.05 (d, 2H), 7.25 (brs, 5H), 7.98 (d, 2H).

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EXAMPLE 21

Starting with 3,3-diethyl-4-acetoxyazetidin-2-one as prepared in Scheme (d) followed by displacement of the acetate with the appropriate phenol and acylation of the nitrogen with the corresponding chiral isocyanate as shown in Scheme (h) and example 20, steps C-E, the following compounds were prepared. The diastereomers obtained on acylation were separated by silica gel chromatography using 10-30% ethylacetate/hexane solvent mixtures.

20 (4S)-3,3-diethyl-1-((R)-α-ethylbenzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.

NMR (CDCl₃): δ 0.9 (t, 3H, J = 7Hz), 0.94 (t, 3H, J = 7Hz), 1.07 (t, 3H, J = 7Hz) 1.65 - 2.05 (m, 6H), 3.58 (s, 2H), 4.8 (q, 1H, J = 8Hz), 5.58 (s, 1H), 7.0 (d, 1H, J = 8Hz), 7.1 - 7.45 (m, 9H)

25 (4S)-3,3-diethyl-1-((R)-α-n-propylbenzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.

NMR (CDCl₃): δ 0.91 (t, 3H, J = 7Hz), 0.94 (t, 3H, J = 7Hz), 1.07 (t, 3H, J = 7Hz) 1.34 (m, 2H), 1.65 - 2.05 (m, 6H), 3.57 (s, 2H), 4.88 (q, 1H, J = 7Hz), 5.58 (s, 1H), 7.0 (d, 1H, J = 7Hz) 7.1 - 7.5 (m, 9H)

30 (4S)-3,3-diethyl-1-((R)-α-allyl-(4-methyl)benzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.

NMR (CDCl₃): δ 0.96 (t, 3H, J = 7Hz), 1.07 (t, 3H, J = 7Hz), 1.7 - 2.1 (m, 4H), 2.32 (s, 3H), 2.57 (t, 2H, J = 7Hz), 3.58 (s, 2H), 4.95 (q, 1H, J = 7Hz), 5.14 (m, 2H), 5.58 (s, 1H), 5.66 (m, 1H), 7.03 (d, 1H, J = 7Hz), 7.16 (s, 4H), 7.19 (s, 4H).

35

(4S)-3,3-diethyl-1-((R)-α-allyl(3,4-methylenedioxy)benzylaminocarbonyl)-4-(4-carboxymethyl)-phenoxyazetidin-2-one.

40 NMR (CDCl₃): δ 0.96 (t, 3H, J = 7Hz), 1.05 (t, 3H, J = 7Hz), 1.65 - 2.05 (m, 4H), 2.54 (t, 2H, J = 6Hz) 4.87 ((q, 1H, J = 7Hz), 5.05 - 5.2 (m, 2H), 5.58 (s, 1H), 5.66 (m, 1H), 5.94 (s, 2H), 6.76 (s, 3H), 6.98 (d, 1H, J = 7Hz), 7.2 (m, 4H)).

45 (4S)-3,3-diethyl-1-((R)-α-n-propyl(3,4-methylenedioxy)-benzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.

NMR (CDCl₃): δ 0.9 (t, 3H, J = 7Hz), 0.94 (t, 3H, J = 7Hz), 1.06 (t, 3H, J = 7Hz), 1.3 (m, 2H), 1.65 - 2.1 (m, 6H), 3.58 (s, 2H), 4.76 (q, 1H, J = 7Hz), 5.58 (s, 1H), 5.92 (s, 2H), 6.15 (s, 3H) 6.88 (d, 1H, J = 7Hz), 7.2 (m, 4H).

50 (4S)-3,3-diethyl-1-((R)-α-n-propyl(4-methyl)benzylaminocarbonyl)-4-(4-carboxy)phenoxyazetidin-2-one.

NMR (CDCl₃): δ 0.91 (t, 3H, J = 7Hz), 0.98 (t, 3H, J = 7Hz), 1.07 (t, 3H, J = 7Hz) 1.32 (m, 2H), 1.65 - 2.1 (m, 6H), 2.33 (s, 3H), 4.83 (q, 1H, J = 7Hz), 5.71 (s, 1H), 6.93 (d, 1H, J = 7Hz), 7.16 (s, 4H), 7.25 (d, 2H, J = 8Hz), 8.04 (d, 2H, J = 8Hz).

55 (4S)-3,3-diethyl-1-((R)-α-n-propyl(4-methyl)benzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.

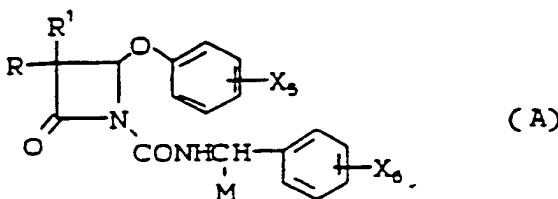
NMR (CDCl₃): δ 0.9 (t, 3H, J = 7Hz), 0.93 (t, 3H, J = 7Hz), 1.07 (t, 3H, J = 7Hz) 1.28 (m, 2H), 1.7 - 2.1 (m, 6H), 2.33 (s, 2H), 3.6 (s, 2H), 4.81 (q, 1H, J = 7Hz), 5.56 (s, 1H), 6.93 (d, 1H, J = 7Hz), 7.15 (s, 4H), 7.2 (s, 4H).

Claims

1. A compound of the formula (A)

5

10



wherein:

15 R and R' independently are C₁-₆ alkyl or C₁-₆ alkoxy C₁-₆ alkyl;

M is

(1) hydrogen,

(2) C₁-₆ alkyl,

(3) C₂-₅ alkenyl, or

(4) C₁-₆ alkoxy C₁-₆ alkyl;

20 X₅ is

(1) hydrogen,

(2) C₁-₆ alkyl,

(3) halo C₁-₆ alkyl,

(4) C₂-₅ alkenyl,

(5) C₂-₅ alkynyl,

(6) carboxy,

(7) carboxy-C₁-₆ alkyl,

(8) carboxy-C₁-₆ alkylcarbonyl,

(9) carboxy-C₁-₆ alkylcarbonylamino,

30 (10) carboxy-C₂-₅ alkenyl,

(11) hydroxy-C₁-₆ alkyl,

(12) C₁-₆ alkylcarbonyl,

(13) C₁-₆ alkylcarbonylamino, or

35 (14) di-(C₁-₆ alkyl)amino-C₁-₆ alkyl; and

X₅ is

(1) hydrogen,

(2) C₁-₆ alkyl,

(3) halo

(4) carboxy,

(5) C₁-₆ alkoxy,

(6) phenyl,

(7) C₁-₆ alkylcarbonyl,

(8) di-(C₁-₆ alkyl)amino,

(9) phenoxy,

45 (10) methylenedioxy,

(11) 2,3-furanyl, or

(12) 2,3-thienyl; or

a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein:

50 R and R' independently are C₁-₆ alkyl;
and

X₅ is carboxy or carboxy-C₁-₆ alkyl.

3. A compound of Claim 2 wherein:

M is C₁-₃ alkyl or allyl; and

55 X₅ is hydrogen, C₁-₆ alkyl, or 3,4-methylenedioxy or phenyl.

4. A compound of Claim 3 wherein:
 R is ethyl; and
 R' is methyl or ethyl.

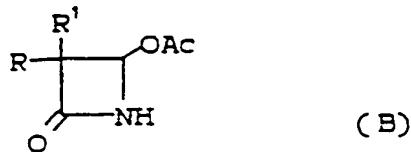
5. A compound of Claim 4 wherein:
 5 R and R' are ethyl;
 M is n-propyl;
 X₅ is 4-carboxymethyl; and
 X₆ is 4-methyl.

6. A pharmaceutical composition for the inhibition of human leukocyte elastase which comprises a
 10 nontoxic therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

7. A composition of Claim 6 wherein:
 R is ethyl;
 R' is methyl or ethyl;
 15 M is C₁-₅ alkyl or allyl;
 X₅ is carboxy or carboxy-C₁-₅ alkyl;
 and
 X₆ is hydrogen C₁-₅ alkyl, 3,4-methylenedioxy or phenyl.

8. A composition of Claim 7 wherein:
 20 R' is ethyl;
 M is n-propyl;
 X₅ is 4-carboxymethyl; and
 X₆ is 4-methyl.

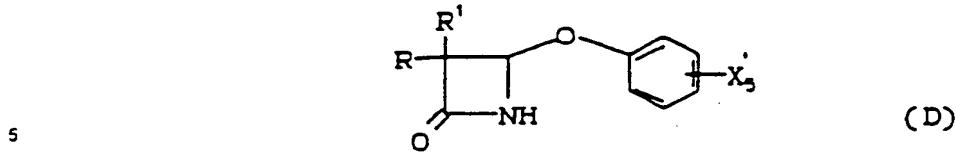
9. A process for the preparation of the compounds of Claim 1 which comprises
 25 (1) reacting a compound of the following formula (B)



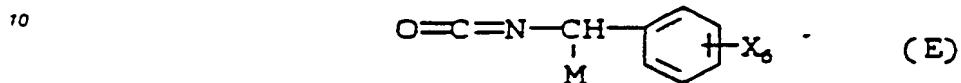
with a compound of the formula (C)



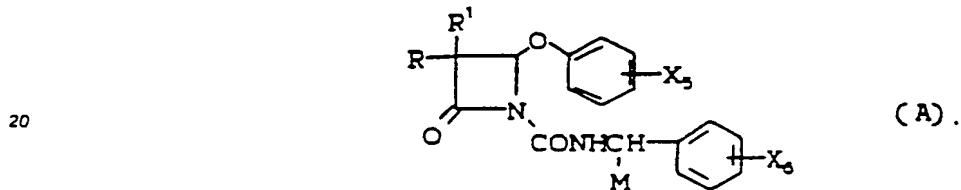
40 wherein X₅ is
 (1) hydrogen
 (2) C₁-₅ alkyl,
 (3) halo-C₁-₅ alkyl,
 (4) C₂-₅ alkenyl,
 45 (5) C₂-₅ alkynyl,
 (6) C₁-₅ alkoxy carbonyl,
 (7) C₁-₅ alkoxy carbonyl-C₁-₅ alkyl,
 (8) C₁-₅ alkoxy carbonyl-C₁-₅ alkyl carbonyl,
 50 (9) C₁-₅ alkoxy carbonyl-C₁-₅ alkyl carbonyl amino,
 (10) C₁-₅ alkoxy carbonyl-C₂-₅ alkenyl,
 (11) hydroxy alkyl,
 (12) C₁-₅ alkyl carbonyl,
 (13) C₁-₅ alkyl carbonyl amino, or
 55 (14) di-(C₁-₅ alkyl)amino-C₁-₅ alkyl under basic conditions to afford a compound of the formula (D)



and (2) reacting compound (D) with a compound of the formula (E)



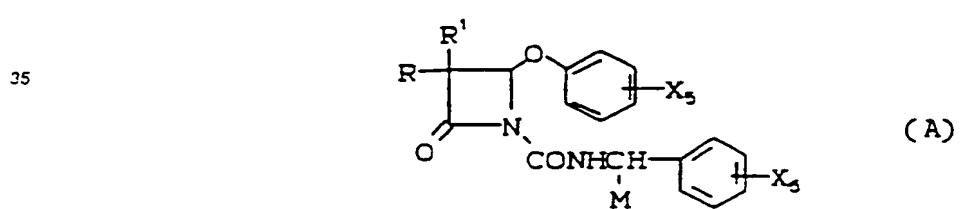
15 under basic conditions, and optionally converting X5' into X5, to yield the compound of the formula (A)



25 10. A process of Claim 9 wherein:

Step (1) is in the presence of an alkali metal hydroxide.
Step (2) is in the presence of a tri(C₁-₅ alkyl)-amine; and
the conversion of X5' into X5 is accomplished in the presence of a strong acid.
Claims for the following Contracting States: ES and GR

30 1. A process for the preparation of a compound of the formula (A)



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wherein:

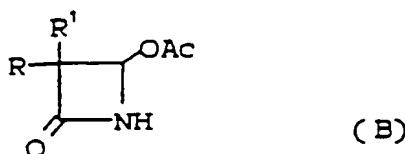
R and R' independently are C₁-₅ alkyl or C₁-₅ alkoxy C₁-₅ alkyl;
M is

45 (1) hydrogen,
(2) C₁-₅ alkyl,
(3) C₂-₅ alkenyl, or
(4) C₁-₅ alkoxy-C₁-₅ alkyl;

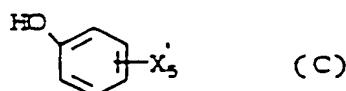
X5 is

50 (1) hydrogen,
(2) C₁-₅ alkyl,
(3) halo C₁-₅ alkyl,
(4) C₂-₅ alkenyl,
(5) C₂-₅ alkynyl,
55 (6) carboxy,
(7) carboxy-C₁-₅ alkyl,
(8) carboxy-C₁-₅ alkylcarbonyl,
(9) carboxy-C₁-₅ alkylcarbonylamino.

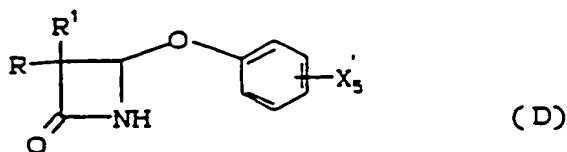
(10) carboxy-C₂-_s alkenyl,
 (11) hydroxy-C₁-_s alkyl,
 (12) C₁-_s alkylcarbonyl,
 (13) C₁-_s alkylcarbonylamino, or
 5 (14) di-(C₁-_s alkyl)amino-C₁-_s alkyl; and
 X₆ is
 (1) hydrogen,
 (2) C₁-_s alkyl,
 (3) halo
 10 (4) carboxy,
 (5) C₁-_s alkoxy,
 (6) phenyl,
 (7) C₁-_s alkylcarbonyl,
 (8) di-(C₁-_s alkyl)amino.
 15 (9) phenoxy,
 (10) methylenedioxy,
 (11) 2,3-furanyl, or
 (12) 2,3-thienyl; or
 a pharmaceutically acceptable salt thereof which comprises
 20 (1) reacting a compound of the following formula (B)



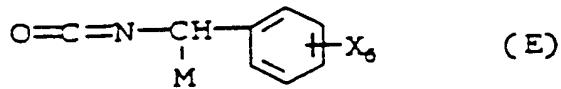
with a compound of the formula (C)



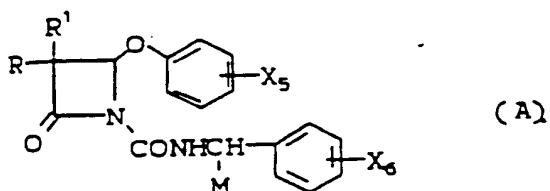
35 wherein X₅ is
 (1) hydrogen
 (2) C₁-_s alkyl,
 (3) halo-C₁-_s alkyl,
 (4) C₂-_s alkenyl,
 40 (5) C₂-_s alkynyl,
 (6) C₁-_s alkoxy carbonyl,
 (7) C₁-_s alkoxy carbonyl-C₁-_s alkyl,
 (8) C₁-_s alkoxy carbonyl-C₁-_s alkyl carbonyl,
 45 (9) C₁-_s alkoxy carbonyl-C₁-_s alkyl carbonyl amino,
 (10) C₁-_s alkoxy carbonyl-C₂-_s alkenyl,
 (11) hydroxy alkyl,
 (12) C₁-_s alkyl carbonyl,
 (13) C₁-_s alkyl carbonyl amino, or
 50 (14) di-(C₁-_s alkyl)amino-C₁-_s alkyl
 under basic conditions to afford a compound of the formula (D)



and (2) reacting compound (D) with a compound of the formula (E)



under basic conditions, and optionally converting X_5' into X_5 , to yield the compound of the formula (A)



2. A process of Claim 1 wherein:

R and R' independently are C_{1-6} alkyl; and

X_5 is carboxy or carboxy C_{1-6} alkyl.

20 3. A process of Claim 2 wherein:

M is C_{1-3} alkyl or allyl; and

X_6 is hydrogen, C_{1-6} alkyl, or 3,4-methylenedioxy or phenyl.

4. A process of Claim 3 wherein:

25 R is ethyl; and

R' is methyl or ethyl.

5. A process of Claim 4 wherein:

R and R' are ethyl;

M is n-propyl;

30 X_5 is 4-carboxymethyl; and

X_6 is 4-methyl.

6. A process of Claim 1 wherein:

Step (1) is in the presence of an alkali metal hydroxide;

Step (2) is in the presence of a tri(C_{1-6} alkyl)amine; and

35 the conversion of X_5' into X_5 is accomplished in the presence of a strong acid.

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European Patent
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EUROPEAN SEARCH REPORT

Application number

EP 89200864.0

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.)
X	<u>EP - A1 - 0 199 630</u> (MERCK) * Claims 1,9 * -----	1-9	C 07 D 205/08 A 61 K 31/395
TECHNICAL FIELDS SEARCHED (Int. Cl.)			
C 07 D 205/00			
The present search report has been drawn up for all claims			
Place of search VIENNA	Date of completion of the search 14-07-1989	Examiner JANISCH	
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